



Spontaneous ecological recovery of vegetation in a red gypsum landfill: *Betula pendula* dominates after 10 years of inactivity

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

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Abstract.

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

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

Results. Antibiotics were stopped during 62 febrile neutropaenia episodes, and maintained in the control group (n=13). Median age was 54 years. 39 (63%) patients received induction and 23 (37) consolidation chemotherapy. 36 (58%) patients had fever of unknown origin. Median neutropaenia length was 26 days [IQR 24–30]. Antibiotics were started at day 9 [5–13]. Most patients received piperacillin-tazobactam (56%) or cefepime (32%). Antimicrobial therapy was longer in the control group compared with the policy compliant group, 10 [7–16] vs. 19 days [15–23], $p=0.0001$. After antibiotics discontinuation, 20% patients experienced fever recurrence, within 5.5 days [3–7.5]. None of these febrile episodes were severe. 80% patients remained afebrile, with neutrophil recovery occurring within five days [2–8.5]. Overall, 287 antibiotics days were spared; this represents 49% of all days with antibiotics. No patient had died at day 30 from intervention; six died during late follow-up, two from Graft-versus-Host disease and four from relapsed or refractory leukaemia.

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

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

1. Introduction.

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

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

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

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

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

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

2. Material and methods.

2.1 Population.

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

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

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

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

2.2 Antimicrobial therapy discontinuation.

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

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

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

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

2.3 Endpoint.

Our primary endpoint was the occurrence of a new febrile episode after AMT discontinuation. Secondary endpoints were number of days without antibiotics, occurrence of severe 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

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

3.2 Population.

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

3.3 Control group.

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

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

3.4 Febrile neutropaenia.

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

3.5 Antimicrobial therapy.

Empirical AMT was initiated immediately after the first episode of FN. Four patients (6%) received cefotaxime as monotherapy (100mg/kg/day IV divided in 3 doses). Most patients 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 carbapenem, 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.

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254

255

3.6 Outcome.

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

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

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

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

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

3.7 Mortality.

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

4. Discussion.

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

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

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

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

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

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

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

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

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

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

5. Conclusions.

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

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433 Ethical Approval: Not required

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

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Fig. 1.

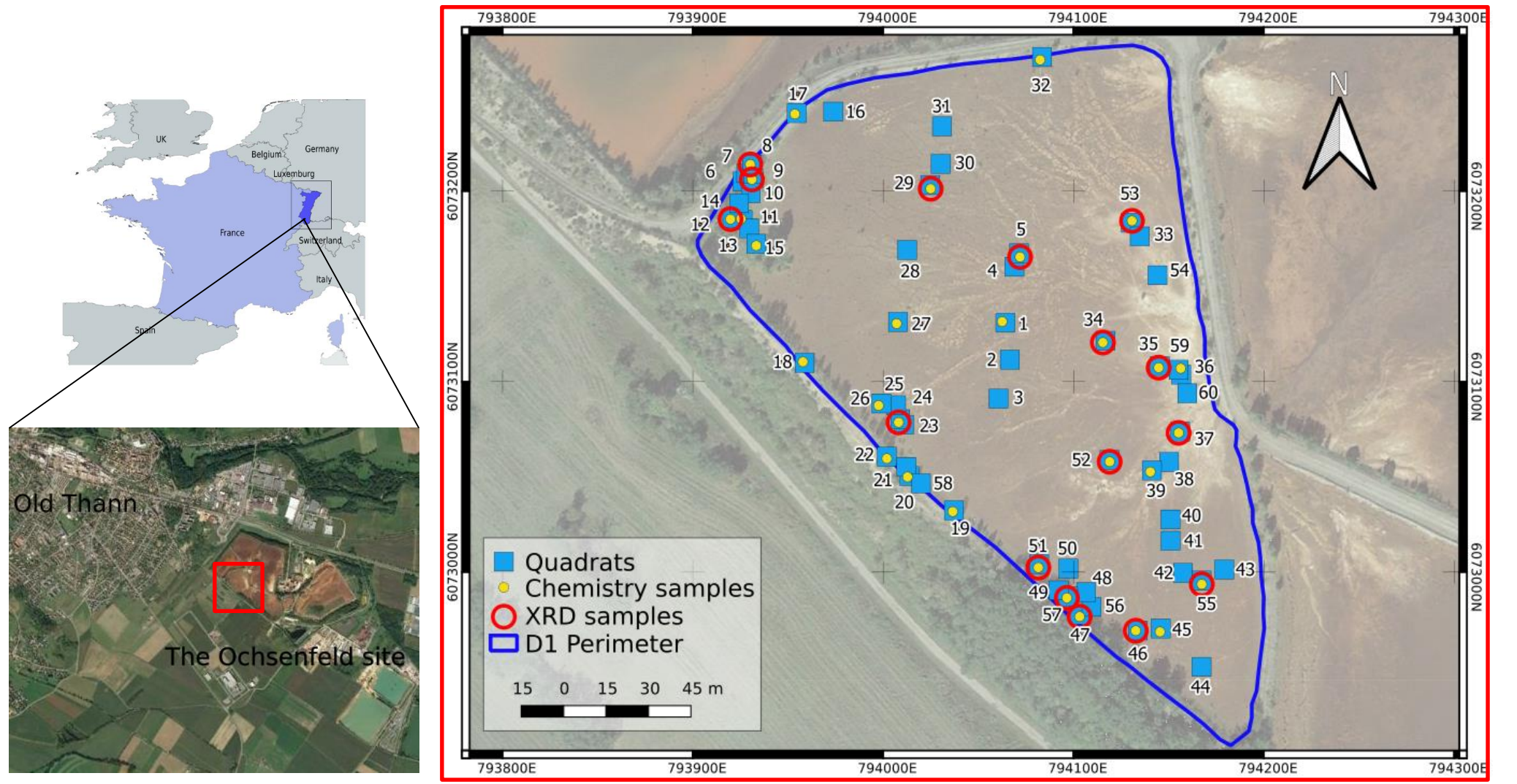
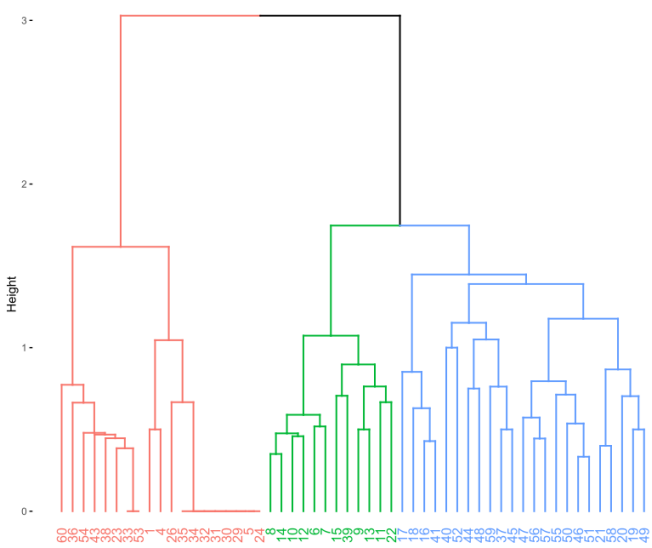


Fig. 2.

A)



B)

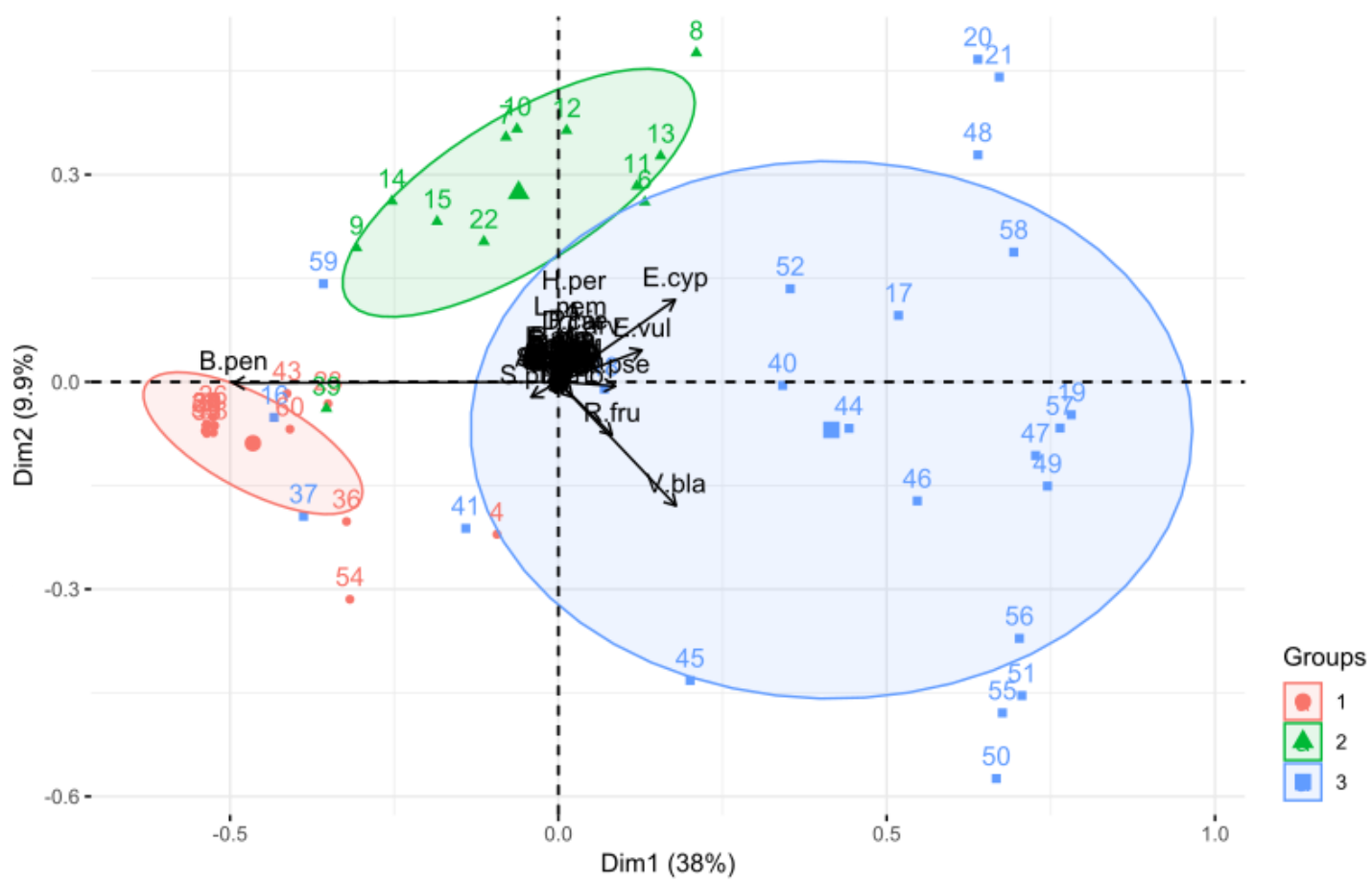


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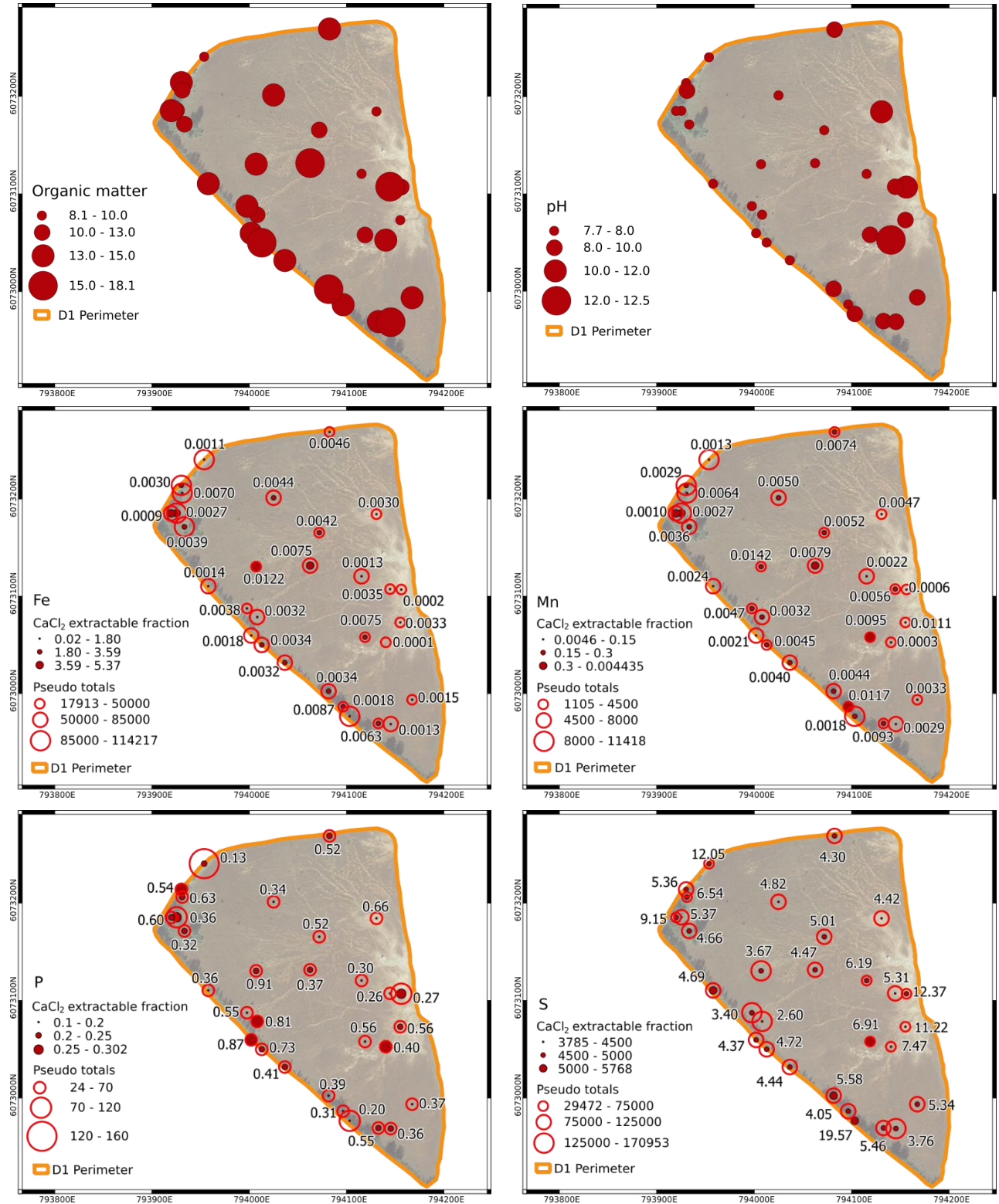


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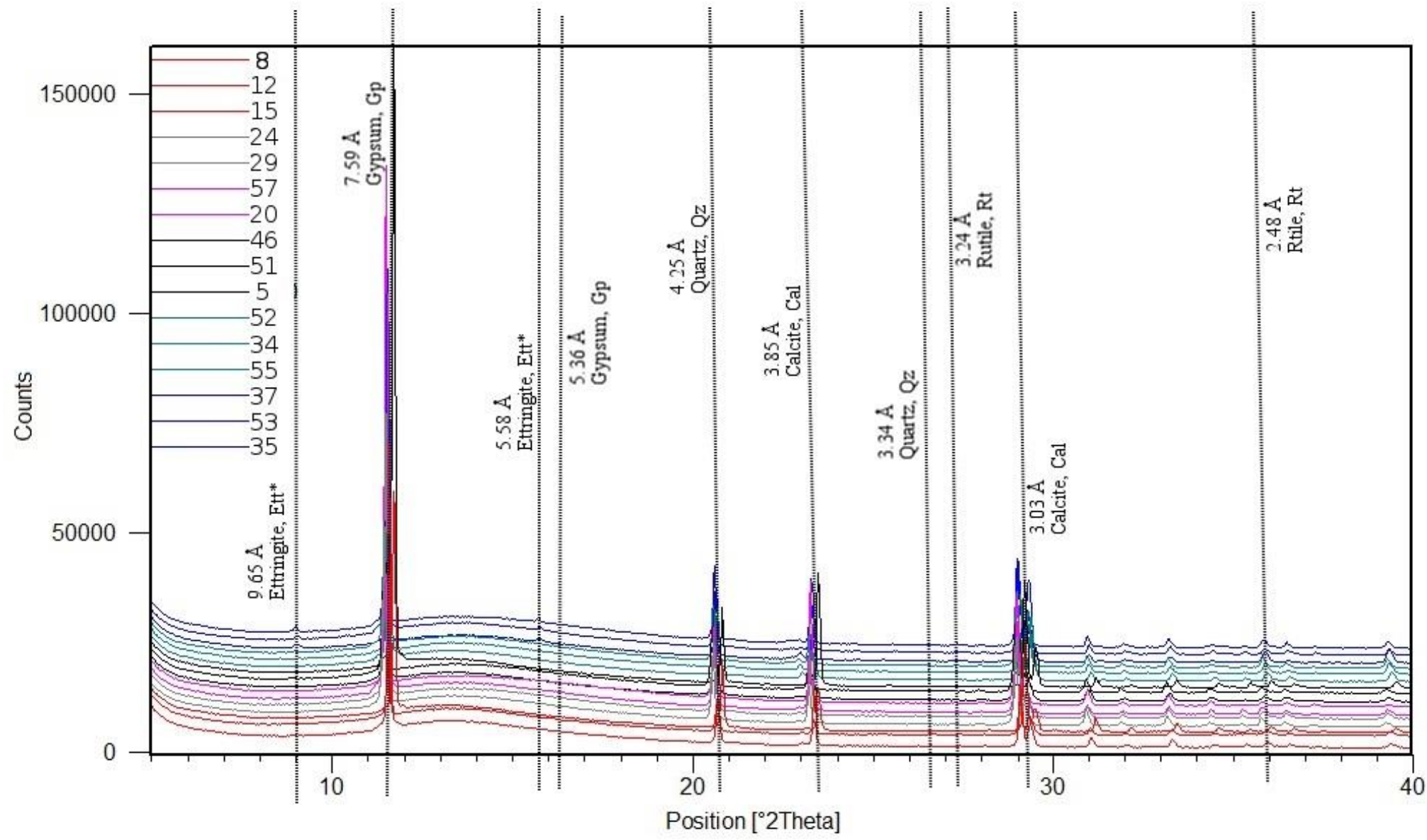


Fig. 5.

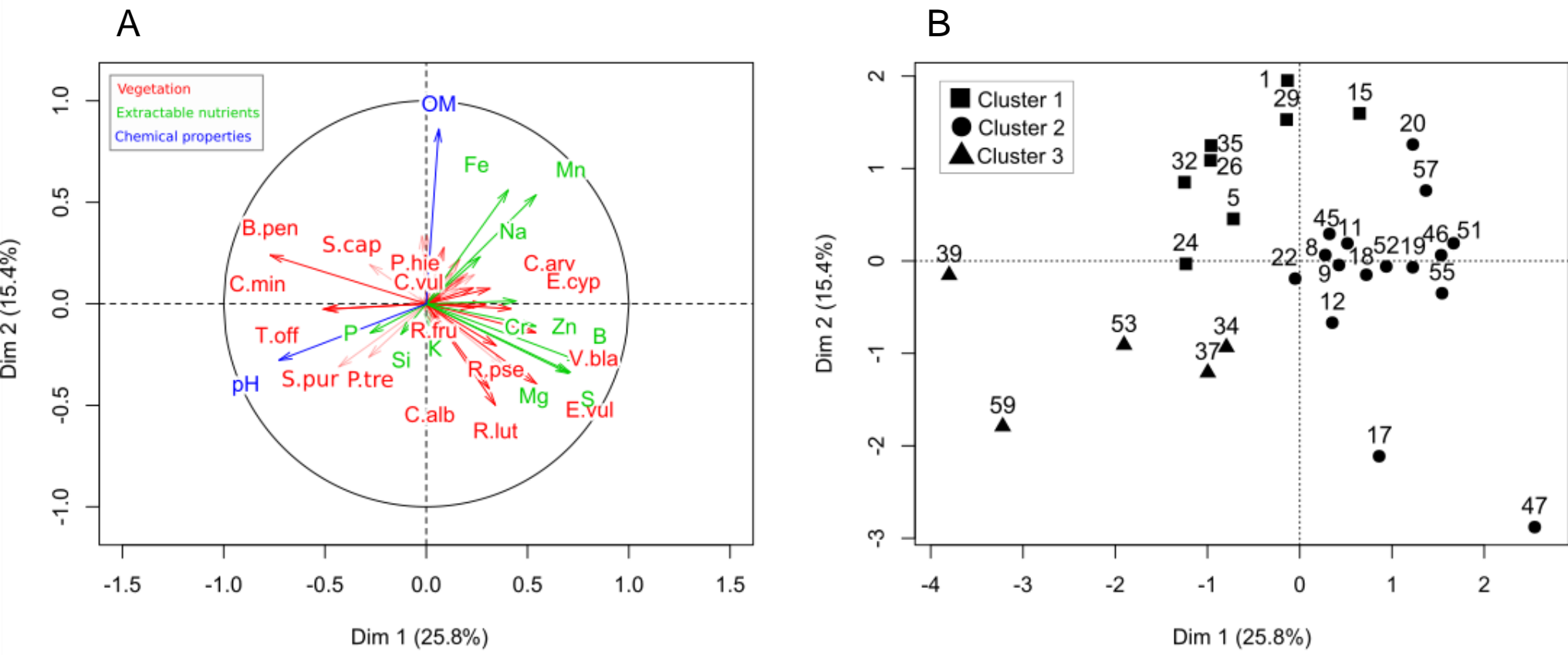


Table 1

Family	Genus	Species	ID	Family	Genus	Species	ID
<i>Adoxaceae</i>	<i>Sambucus</i>	<i>nigra</i>	<i>S.nig</i>	<i>Onagraceae</i>	<i>Epilobium</i>	<i>angusifolium</i>	<i>E.aun</i>
<i>Amaranthaceae</i>	<i>Beta</i>	<i>sp</i>	<i>B.sp</i>	<i>Onagraceae</i>	<i>Epilobium</i>	<i>parviflorum</i>	<i>E.par</i>
<i>Amaranthaceae</i>	<i>Chenopodium</i>	<i>album</i>	<i>C.alb</i>	<i>Papaveraceae</i>	<i>Papaver</i>	<i>rhoeas</i>	<i>P.rho</i>
<i>Apiaceae</i>	<i>Daucus</i>	<i>carotta</i>	<i>D.car</i>	<i>Plantaginaceae</i>	<i>Chaenorrhinum</i>	<i>minus</i>	<i>C.min</i>
<i>Asteraceae</i>	<i>Artemisia</i>	<i>vulgaris</i>	<i>A.vul</i>	<i>Plantaginaceae</i>	<i>Plantago</i>	<i>lanceolata</i>	<i>P.lan</i>
<i>Asteraceae</i>	<i>Cirsium</i>	<i>arvense</i>	<i>C.arv</i>	<i>Plantaginaceae</i>	<i>Plantago</i>	<i>major</i>	<i>P.maj</i>
<i>Asteraceae</i>	<i>Cirsium</i>	<i>vulgare</i>	<i>C.vul</i>	<i>Poaceae</i>	<i>Bromus</i>	<i>hordaceus</i>	<i>B.hor</i>
<i>Asteraceae</i>	<i>Conyza</i>	<i>canadensis</i>	<i>C.can</i>	<i>Poaceae</i>	<i>Bromus</i>	<i>sterilis</i>	<i>B.ste</i>
<i>Asteraceae</i>	<i>Erigeron</i>	<i>annuus</i>	<i>E.ann</i>	<i>Poaceae</i>	<i>Festuca</i>	<i>pratensis</i>	<i>F.pra</i>
<i>Asteraceae</i>	<i>Hieracium</i>	<i>sp</i>	<i>H.sp</i>	<i>Poaceae</i>	<i>Festuca</i>	<i>rubra</i>	<i>F.rub</i>
<i>Asteraceae</i>	<i>Leontodon</i>	<i>hispidus</i>	<i>L.his</i>	<i>Poaceae</i>	<i>Poa</i>	<i>annua</i>	<i>P.ann</i>
<i>Asteraceae</i>	<i>Matricaria</i>	<i>chamomilla</i>	<i>M.cha</i>	<i>Poaceae</i>	<i>Poa</i>	<i>trivialis</i>	<i>P.tri</i>
<i>Asteraceae</i>	<i>Picris</i>	<i>hieracioides</i>	<i>P.hie</i>	<i>Poaceae</i>	<i>Vulpia</i>	<i>myuros</i>	<i>V.myu</i>
<i>Asteraceae</i>	<i>Pilosella</i>	<i>officinalis</i>	<i>P.off</i>	<i>Primulaceae</i>	<i>Lysimachia</i>	<i>nemorum</i>	<i>L.nem</i>
<i>Asteraceae</i>	<i>Scorzonera</i>	<i>humilis</i>	<i>S.hum</i>	<i>Ranunculaceae</i>	<i>Clematis</i>	<i>vitalba</i>	<i>C.vit</i>
<i>Asteraceae</i>	<i>Sonchus</i>	<i>asper</i>	<i>S.asp</i>	<i>Resedaceae</i>	<i>Reseda</i>	<i>lutea</i>	<i>R.lut</i>
<i>Asteraceae</i>	<i>Taraxacum</i>	<i>officinale</i>	<i>T.off</i>	<i>Rosaceae</i>	<i>Crataegus</i>	<i>laevigata</i>	<i>C.lae</i>
<i>Betulaceae</i>	<i>Betula</i>	<i>pendula</i>	<i>B.pen</i>	<i>Rosaceae</i>	<i>Potentilla</i>	<i>argentea</i>	<i>P.arg</i>
<i>Boraginaceae</i>	<i>Cynoglossum</i>	<i>officinale</i>	<i>C.off</i>	<i>Rosaceae</i>	<i>Prunus</i>	<i>avium</i>	<i>P.avi</i>
<i>Boraginaceae</i>	<i>Echium</i>	<i>vulgare</i>	<i>E.vul</i>	<i>Rosaceae</i>	<i>Rosa</i>	<i>arvensis</i>	<i>R.arv</i>
<i>Caryophyllaceae</i>	<i>Arenaria</i>	<i>serpyllifolia</i>	<i>A.ser</i>	<i>Rosaceae</i>	<i>Rubus</i>	<i>fruticosus</i>	<i>R.fru</i>
<i>Caryophyllaceae</i>	<i>Cerastium</i>	<i>fontanum</i>	<i>C.fon</i>	<i>Rubiaceae</i>	<i>Galium</i>	<i>mollugo</i>	<i>G.mol</i>
<i>Euphorbiaceae</i>	<i>Euphorbia</i>	<i>cyparissias</i>	<i>E.cyp</i>	<i>Salicaceae</i>	<i>Populus</i>	<i>nigrum</i>	<i>P.nig</i>
<i>Fabaceae</i>	<i>Lotus</i>	<i>corniculatus</i>	<i>L.cor</i>	<i>Salicaceae</i>	<i>Populus</i>	<i>tremula</i>	<i>P.tre</i>
<i>Fabaceae</i>	<i>Medicago</i>	<i>indica</i>	<i>M.ind</i>	<i>Salicaceae</i>	<i>Salix</i>	<i>caprea</i>	<i>S.cap</i>
<i>Fabaceae</i>	<i>Medicago</i>	<i>lupulina</i>	<i>M.lup</i>	<i>Salicaceae</i>	<i>Salix</i>	<i>purpurea</i>	<i>S.pur</i>
<i>Fabaceae</i>	<i>Robinia</i>	<i>pseudoacacia</i>	<i>R.Pse</i>	<i>Sapindaceae</i>	<i>Acer</i>	<i>pseudoplatanus</i>	<i>A.pse</i>
<i>Fabaceae</i>	<i>Trifolium</i>	<i>pratense</i>	<i>T.Pra</i>	<i>Scrophulariaceae</i>	<i>Verbascum</i>	<i>blattaria</i>	<i>V.bla</i>
<i>Fabaceae</i>	<i>Vicia</i>	<i>sativa</i>	<i>V.Sat</i>	<i>Verbenaceae</i>	<i>Verbena</i>	<i>officinalis</i>	<i>V.off</i>
<i>Hypericaceae</i>	<i>Hypericum</i>	<i>perforatum</i>	<i>H.per</i>				

