1. Résumé en français

Objectif : Les bactériémies sont responsables d'une morbidité élevée chez les enfants immunodéprimés. La documentation d'une bactériémie demeure difficile en cas de survenue d'un épisode fébrile chez ces patients fragiles, c'est pourquoi une antibiothérapie probabiliste à large spectre est rapidement initiée. L'objectif de cette étude est double. Il consiste à la fois à caractériser l'épidémiologie des bactéries responsables de bactériémie chez des enfants immunodéprimés, mais également d'étudier l'émergence de bactéries résistantes aux antibiotiques chez ces mêmes patients

Méthodes : Une étude descriptive et rétrospective fut menée de janvier 2014 à décembre 2017 à l'institut d'hématologie et d'oncologie pédiatrique de Lyon, un centre unique représentatif de tous les niveaux d'immunodépression de l'enfant. Notre cohorte comprenait des patients atteints de maladies hématologiques et oncologiques, des enfants ayant reçu une greffe de cellules souches hématopoïétiques, et de patients souffrant de déficit immunitaire combiné sévère. Une bactériémie était définie par une hémoculture positive associée à de la fièvre. L'antibiothérapie probabiliste était adaptée au niveau d'immunodépression de l'enfant et à une éventuelle colonisation bactérienne antérieure, et comprenait de la vancomycine, de l'amikacine et une pénicilline à large spectre.

Résultats : 310 (4.2%) bactériémies furent identifiées chez 186 patients sur les 7301 hospitalisations recensées en 4 ans. Les Cocci Gram-Positifs étaient majoritaires et représentaient 72,9 % des bactériémies documentées avec 49.7 % de staphylocoques à coagulase négatifs et 6.5% de *Staphylococcus aureus*. Les Bacilles Gram-Négatifs représentaient 21.6% des pathogènes identifiés avec 4.8% d'infections à *Pseudomonas*. L'incidence annuelle des bactériémies diminua de 0.75% (p =0.002) par an. Seules 11 des 310 bactériémies (3.5%) furent causées par des bactéries multirésistantes.

Conclusion :
Les bactériémies chez les patients immunodéprimés sont majoritairement dues à des Cocci-Gram-Positifs. Dans notre étude, l'utilisation raisonnée d'antibiotiques à large spectre n'était pas associée à l'émergence de bactéries multirésistantes.

2. Résumé en anglais

Objective: Bloodstream infections (BSI) remain a major cause of morbidity and mortality in immunocompromised children. Documenting bacteremia at the onset of fever in immunocompromised patients is problematic: this leads to an early administration of broad-spectrum antibiotics. This study was performed to investigate the epidemiology of BSI: the bacterial spectrum and antibiotic resistance profiles.

Methods: A retrospective, descriptive study was conducted from January 2014 to December 2017, in a tertiary care center in France, Lyon. Our cohort included a large scale of immunocompromised children: hematological malignancies, oncology patients, children undergoing hematopoietic stem cell transplantation, as well as patients with severe combined immunodeficiency syndromes. A BSI was defined by a positive blood culture sample, associated with fever. Empirical antibacterial therapy was adjusted to the immunosuppression risk group, and prior bacterial colonisation. All patients received vancomycin, amikacin and a broad-spectrum penicillin.

Results: We identified 310 (4.2%) BSI episodes among 186 patients, for a total of 7301 hospitalisations. Gram-positive cocci were the most common isolates, 226/310 (72.9%). Coagulase negative staphylococci were identified in 49.7 % (154/310) BSI and *Staphylococcus aureus* caused 6.5% (20/310) infections. None of the latter were methicillin resistant. Gram-negative-bacilli accounted for 21.6% (67/310) isolated bacteria and *Pseudomonas* for 4.8% (15/310). The incidence of BSI annually decreased of 0.75% (p =0.002). Only 11/310 (3.5%) BSIs were caused by multidrug-resistant bacteria (MDRB), none were vancomycin resistant.

Conclusion: BSI in our immunocompromised patients was mainly caused by Gram-positive bacteria. The controlled use of broad-spectrum antibiotics was not associated with the emergence of MDRB.

3. Revue de la littérature

La médecine est une science qui ne cesse d'évoluer et les avancées thérapeutiques des dernières décennies soulèvent de nouveaux enjeux médicaux. Aux bénéfices d'un meilleur contrôle de la maladie sous immunosuppresseurs, d'une guérison au prix de chimiothérapies intensives ou de thérapies ciblées, s'ajoutent les risques infectieux liés à l'immunodépression induite, ou innée. Les polynucléaires neutrophiles jouent un rôle majeur dans l'immunité innée en attaquant les agents bactériens et fongiques, déclenchant ainsi une cascade pro-inflammatoire au site de l'infection. Une neutropénie, qualitative ou quantitative, expose ainsi les patients immunodéprimés à un risque d'infection bactérienne et/ou fongique grave.

L'altération de la fonction immunitaire peut être congénitale, comme cela se retrouve chez les enfants présentant un déficit immunitaire combiné sévère ou bien une granulomatose septique. Elle peut également être secondaire aux corticothérapies prolongées, aux cancers (hématologiques en particulier), aux chimiothérapies, à l'utilisation d'immunodépresseurs au long cours, et aux greffes (de moelle ou d'organe). Cependant, les niveaux d'immunodépression ne sont pas les mêmes pour tous ces patients. Dans cette population hétérogène, une augmentation en nombre et en durée des épisodes de neutropénie fébrile est constatée[1].

En cas de neutropénie fébrile, les bactériémies sont les infections les plus fréquemment documentées (jusqu'à 22%)[2]. Les complications infectieuses demeurent la cause majeure de morbidité chez ces enfants immunodéprimés[2,3]. Ces épisodes infectieux allongent la durée moyenne d'hospitalisation, impactant la qualité de vie des patients et de leurs familles. Les soins engendrés ne sont pas dénués de risques : infections nosocomiales, effets secondaires et toxicité des antibiotiques, retard dans les protocoles de chimiothérapie… Ces épisodes infectieux entraînent un surcoût médico-économique[4].

Dans les pays développés, la mortalité liée à ces infections bactériennes demeure basse. Dans son étude prospective multicentrique, réalisée dans 8 instituts d'oncologie pédiatrique allemands et suisses, de 2007 à 2010, Ammann *et al*. rapportent 3 décès (1,8% ; 3/179) attribuables aux septicémies. Un des pathogènes identifiés était un *Enterobacter cloacae* sécréteur de bêtalactamase à spectre élargi résistant au traitement de première ligne par pipéracilline - tazobactam et gentamicine[4]. Une étude plus ancienne de L'European Organisation for Research and Treatment of Cancer (EORTC) comparant les bactériémies chez

les enfants et les adultes immunodéprimés rapporte une mortalité liée aux infections de 1% chez les enfants contre 4% chez les adultes (p=0,001)[5].

Pour mémoire, les infections fongiques opportunistes (*Candida, Aspergillus, Mucorales*) peuvent également être à l'origine de tableaux sévères chez ces enfants immunodéprimés, notamment pour ceux ayant une neutropénie profonde et prolongée. En cas d'infection invasive à *Aspergillus*, le taux de survie était de 58% (étude de 2001-2010) dans une étude française [6]. Ce taux chutait drastiquement en cas d'infection mucorale. Une origine infectieuse virale ou encore parasitaire ne doit cependant pas être oubliée en fonction du contexte clinique.

De plus en plus de pédiatres sont amenés à prendre en charge ces épisodes fébriles, voire infectieux, dans cette population hétérogène d'enfants immunodéprimés. L'objectif étant de soigner, tout en minimisant l'échec clinique, la toxicité thérapeutique et la sélection de souches bactériennes résistantes.

DEFINITIONS :

Il faut dans un premier temps identifier et définir ces situations à risque. A l'heure actuelle, il n'existe pas en France ou à l'international de consensus exact sur la définition de Neutropénie Fébrile (NF) chez ces enfants immunodéprimés[1]. Selon l'Infectious Diseases Society of America (IDSA), la neutropénie fébrile (NF) est définie par une température orale $\geq 38{,}3°C$ une fois, ou bien $\geq 38°C$ pendant une durée > 1 heure. Le chiffre de polynucléaires neutrophiles (PNN) doit être inférieur à 500/mm^3 ou pouvant le devenir dans les prochaines 48 heures. Pour la Société Européenne d'Oncologie Médicale (ESMO), la NF associe une fièvre $> 38{,}5°C$ en une seule prise ou $> 38°C$ en deux prises à un intervalle de deux heures, associée à un compte de PNN inférieur à 500/mm^3 ou pouvant le devenir[1]. Le risque d'infection devient majeur si les PNN sont < 100/mm^3.

EPIDEMIOLOGIE :

Seules 40 à 50% des NF sont d'origine infectieuse, et 10 à 30 % seront documentées par une bactériémie [7]. Toutefois, l'introduction d'une antibiothérapie probabiliste à large spectre demeure une urgence. Il n'existe pas à ce jour de test clinico-biologique sensible et spécifique permettant de différencier les NF bactériémiques des autres. Le choix d'un traitement empirique exige d'une part une connaissance fine et actualisée du spectre microbiologique en cause dans

les septicémies des patients immunodéprimés. D'autre part, il faut identifier les facteurs de risque propres à l'hôte : portes d'entrée infectieuses (muqueuses ORL et digestives, voie veineuse centrale), antécédents de portages ou de bactériémies à germes multi-résistants, compétences immunologiques de l'hôte (pathologie sous-jacente, phase de chimiothérapie, profondeur et durée de la neutropénie, existence d'une réaction du greffon contre l'hôte en cas de greffe). Chez cette population, les bactéries responsables de septicémies sont souvent issues de leur propre flore (nasopharynx, intestin, peau) constituant un réservoir endogène et exogène[7].

L'épidémiologie des agents pathogènes responsables des bactériémies est en constante évolution géographique et temporelle. Depuis les années 1970, on observe en Europe, un glissement du spectre bactérien des septicémies chez les patients atteints de neutropénie fébrile, des Gram-Négatifs (GN) aux Gram-Positifs (GP)[8]. Les staphylocoques à coagulase négative (CoNS) sont majoritaires, dont plus de la moitié sont résistants à la méthicilline. Les causes de cette modification écologique sont plurifactorielles : l'utilisation d'antibiothérapie prophylactique, la décontamination digestive, la présence de voies veineuses centrales au long cours, l'altération de la barrière cutanéomuqueuse (mucites) induite par les chimiothérapies de plus en plus agressives, l'utilisation d'antibiotiques à large spectre sélectionnant les Cocci Gram-Positifs (CGP). Concernant les bactéries à Gram Négatifs (BGN) , *Escherichia coli* est la plus fréquemment identifiée dans les bactériémies symptomatiques, devant les entérobactéries et *Pseudomonas aeruginosa* (6-7% selon les études)[2,3]. De récentes études menées en Allemagne, aux Pays-Bas et en Suisse sur les bactériémies lors de NF, ont montré des taux bas de bactéries multi-résistantes aux antibiotiques utilisés en routine (*Staphylococcus aureus* résistant à la méthicilline, entérocoques résistants à la vancomycine, BLSE) [3,9].

Toutefois les bactéries circulent facilement à l'ère de la mondialisation et des transports aériens : il faut donc s'intéresser également à l'épidémiologie bactérienne des autres continents. Avec 70% de la population mondiale vivant en Asie/Pacifique, cette région est devenue un épicentre des résistances bactériennes. Une étude sur les bactériémies, menée en Inde en 2013 dans une unité d'oncologie pédiatrique, rapporte des taux alarmants de bactéries multirésistantes. Soixante-et-onze pour cent des pathogènes identifiés étaient des GN avec 24% de bactéries sécrétrices de bêtalactamases à spectre élargi (BLSE) et 26,9% de résistances aux carbapénèmes. La moitié des *Klebsielle* était résistante aux carbapénèmes (probablement NDM-1) ; 41,6% des staphylocoques dorés étaient résistants à la méthicilline [8].

Une étude italienne publiée en 2014 est également alarmante. Caselli *et al*. ont réalisé

une étude rétrospective multicentrique (2000-2008) dans 12 centres d'oncologie pédiatrique. Cent-vingt-sept enfants avaient une bactériémie à *Pseudomonas aeruginosa.* : 31% (39/127) des souches étaient multi-résistantes (résistance à la pipéracilline, aux céphalosporines, aux carbapénèmes et aux fluorochinolones). La mortalité était de 36% (14/39) en cas de résistance bactérienne aux antibiotiques contre 13% (11/88) en l'absence de résistance.

ANTIBIOTHERAPIE :

L'antibiothérapie probabiliste initiale doit donc être adaptée au niveau d'immunodépression ainsi qu'à cette nouvelle écologie : elle doit couvrir les pathogènes majoritaires : les GP, tels que les staphylocoques CoNS et les streptocoques du groupe viridans. Cependant, à cause de la morbidité et de la mortalité élevée associée aux bactériémies à GN, l'antibiothérapie probabiliste doit également couvrir ces pathogènes. En effet en cas de NF et bactériémie à GN, la mortalité peut atteindre 70%[7].

Il existe peu de recommandations mais de nombreux protocoles locaux concernant le choix de la stratégie antibiotique en cas de survenue d'aplasie fébrile en pédiatrie. En 2012 et 2017, un panel international d'experts en oncologie pédiatrique et en maladies infectieuses ont rédigé des recommandations concernant la prise en charge des neutropénies fébriles chez des enfants atteints de cancer et/ou bénéficiant d'une greffe de cellules souches hématopoïétiques[10]. Ce travail avait pour objectif d'établir des recommandations solides pour la prise en charge pédiatrique des neutropénies fébriles. Il existe en effet une hétérogénéité dans les pratiques françaises concernant la prise en charge initiale des neutropénies fébriles.[1]. Ces recommandations proposaient chez les patients à haut risque de NF l'usage d'une monothérapie à large spectre (bêtalactamine active sur le *Pseudomonas* : carbapénème ou céphalosporine de 4ème génération) en première intention en l'absence de sepsis (recommandation forte). Un second antibiotique actif sur les agents GN ou un glycopeptide doit-être administré dans les formes septicémiques/instables ou bien dans les unités à haut taux de résistances bactériennes. En effet, une revue systématique des études cliniques randomisées en cas de NF (3 études avaient des patients à haut risque de NF) comparant une monothérapie *vs* une combinaison avec adjonction d'un aminoglycoside ne montrait pas de différence significative en terme d'échec thérapeutique et de mortalité[10]. Lorsque le risque de NF est faible, ils recommandent (recommandation faible) une antibiothérapie orale. En France, en 2016, seuls 9 centres d'hématologie pédiatrique de la Société Française de Lutte contre les Cancers et Leucémies de

l'Enfant et de l'Adolescent sur 30 (30%) mettaient en pratique cette approche pour les patients neutropéniques fébriles sans sepsis[1].

Dans ce travail de thèse, notre objectif principal a donc été d'étudier l'épidémiologie des bactériémies chez des enfants ayant des niveaux d'immunodépressions différents, allant de patients traités pour des tumeurs solides (faible niveau d'immunodépression) à des patients bénéficiant d'une allogreffe de moelle osseuse (fort niveau d'immunodépression). Notre second objectif a été d'étudier l'existence de résistances bactériennes aux antibiotiques dans notre centre, de 2014 à 2017 inclus.

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4. Contributions des auteurs du travail

Mme Raad et Dr Domenech ont conçu et mené l'étude, collecté les données, analysé les résultats, rédigé, révisé et édité le manuscrit.

Drs Fuhrmann, Grando, Rasigade et Mme Bruchon ont collecté les données, analysé les résultats, et révisé le manuscrit.

Drs Cuzzubbo, Faure-Conter, Garnier, Bergeron, Renard et Bertrand ont collecté et interprété les données et révisé le manuscrit.

Dr Behdenna a réalisé et interprété les analyses statistiques et révisé le manuscrit.

5. Statut de l'article

L'article est en révision dans le journal Eurosurveillance (IF 7, SIGAPS A).

6. Manuscrit

Bloodstream infections in immunocompromised children and emergence of multi-resistant bacteria, Lyon, France, from 2014 to 2017

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INTRODUCTION:

Thanks to the many therapeutic advances made in recent decades, the outcome of immunocompromised children has greatly improved. An alteration in the child's immune system can be caused by either a congenital disease, such as severe combined immunodeficiency syndrome, or can be acquired: hematological malignancies, solid tumors, chemotherapy, and radiotherapy. For all these immunocompromised children, bacterial bloodstream infections (BSI) remain a leading cause of morbidity and mortality (1,2). These BSIs account for nearly half of all nosocomial identified infections (3).

The epidemiology of bacteria causing BSIs has shifted from Gram-Negative organisms in the 1970s to Gram-Positive organisms over the last years (4). BSIs also increase the length of hospitalisation, affect the quality of life of both children and their families and generate significant health costs (5). Thus, many measures are implemented to prevent such events, including antibacterial prophylaxis and early administration of broad-spectrum antibiotic therapy adapted to risk stratification in case of fever. Indeed, the difficulty of documenting bacteremia at the onset of fever in immunocompromised patients led to an early administration

of broad-spectrum antibiotics, without waiting for further clinical or microbiological evidence of infection. The introduction of an empirical antibiotic therapy in febrile neutropenia has reduced the morbidity of infectious complications but differs among pediatric care units (1,2). Antimicrobial resistance occurs naturally over time, and the rapid development of multidrug resistant bacteria (MDRB) has become a major health care issue worldwide. Does our practice trigger the emergence of MDRB?

In this study, we report four years of experience in our tertiary center. Our pluridisciplinary center takes care of patients with congenital immunodeficiency, as well as immunocompromised children induced by chemotherapy for cancer (solid tumor, or hemopathy) and/or HSCT. Our first objective was to analyse the incidence and microbiological spectrum of bacteria-related BSIs. The second objective was to assess if our current large spectrum prophylactic antibiotics protocol led to emergence of MDRB.

METHODS:

Study design and setting

We conducted a monocentric, retrospective and descriptive study over a 4-year period from January 2014 to December 2017. The patients were all treated at the Institute of Pediatric Hematology and Oncology in Lyon, France. This institute is unique in France: it treats children and young adults for hematological diseases (malignancies, severe combined immunodeficiency), solid tumors and has a bone marrow transplantation unit.

All hospitalised patients with a documented BSI were included. Patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) including first line therapy as well as relapse, were treated according to the national and european trials (3,5–7). Patients suffering from malignant lymphomas and solid tumors were treated according to the current ongoing protocols (8–14).

HSCT (allogeneic and autologous) were performed according to the French Society of Bone Marrow Transplantation recommendations. Most patients received a myeloablative conditioning regimen with either total body irradiation or busulfan. Allogeneic HSCT was performed in high-risk acute leukemias in first complete remission, after leukemia relapses, in haemoglobinopathies, in metabolic disorders, in severe combined immunodeficiency syndromes and in aplastic anaemias. Autologous HSCT was performed in high risk solid tumors**.**

Risk stratification of immunocompromised children

The children were divided into 4 infectious risk groups regarding their immunosuppression level. The lower risk group, group 1, included patients with solid tumors, Hodgkin lymphoma and Langerhans cell histiocytosis. Group 2 included patients with low or

medium risk ALL, localised Burkitt lymphoma, lymphoblastic lymphoma, and high-risk neuroblastoma. In group 3 were included the patients with high risk ALL, high-risk Burkitt leukemia/lymphoma. Group 4 representing the highest risk group, included patients treated for AML, infants under 1-year old with ALL, ALL relapses, allogeneic and autologous HSCT, aplastic anemias, severe combined immunodeficiency syndrome.

Supportive care

Our center has 2 different units (protected unit and conventional unit) with dedicated protective isolation methods. The highest isolation measures were taken for the most immunocompromised patients, group 4. Our protected unit was already described (15). Briefly, this unit consisted of positive air pressure single rooms equipped with HEPA filters. Patients were cared for in a clean non-sterile outfit (gowns and mask). Non-sterile gloves were only required with contagious patients. Food restrictions were extended to a low microbial diet. Upon entering the unit, hands were washed with soap and water followed by an alcohol-based rub. Thereafter, only alcohol-based hand rub was used before being in contact with the patient.

Children hospitalised in the conventional unit were isolated in single rooms only if they had contagious disease. The other patients were free to wander in the unit or in collective areas of the hospital: the school, the playground, the main lobby. Alcohol-based hand rub was used by caregivers before and after any contact with patients.

Children in group 3 and 4 received non-absorbable antibiotics for gut and gum decontamination. Gut and gum decontamination were performed with a Gram-negative bacilli (GNB) targeting aminoglycoside (gentamycin). Gum decontamination targeted alpha-hemolytic streptococcus through vancomycin mouthwash (16). Antifungal decontamination was conducted using oral amphotericin B. Gut and gum samples were collected regularly, in

group 2, 3 and 4 and at arrival for group 1 patient previously treated in a foreign hospital. This monitoring was conducted to assess microbial flora characteristic, inquire colonisation with MDRB, and guide empiric antibiotic therapy in the occurrence of fever. No primary antifungal prophylaxis was used for our patients, including group 3 and 4.

All patients had a long-term central venous access device (CVAD) implanted at the diagnosis. Tunneled catheters and peripherally inserted central catheters (PICCs) were cared accordingly to protocol. Clinically infected (local inflammatory signs, pain, redness, swelling, purulent drainage) central venous access devices were removed. Positive blood cultures despite an adapted antibiotic therapy was an indication of CVAD removal. In the occurrence of a *Staphylococcus aureus* related BSIs, CVAD removal was strongly discussed. The presence of *Pseudomonas* or *Stenotrophomonas* related BSIs was an absolute indication for CVAD removal.

Data collection and definitions

Microbiological records were reviewed to identify patients with BSIs. Their medical records were analysed. The patient's legal guardian signed an informed consent before treatment, which included authorisation for the report of their data.

A bacteremia was defined by a positive blood culture sample obtained through a CVAD, associated with fever. For coagulase-negative staphylococci (CoNS) two distinct positive blood cultures within 48 h were mandatory. A polymicrobial infection was defined by a positive blood culture with different pathogens. Fever was defined as a single body temperature > 38.5°C or at least two measures > 38°C in an interval of 1 hour. Neutropenia was defined as an absolute neutrophil count of < 0.5 Giga/L.

Multidrug resistant bacteria were defined as having acquired non-susceptibility to at least one antimicrobial agent in three or more antimicrobial categories. Highly resistant bacteria were defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories. (17)

Empirical intravenous antibiotic therapy protocols

All patients with a CVAD and febrile neutropenia were empirically treated with a glycopeptid (vancomycin), an aminoglycoside (amikacin) and a broad-spectrum penicillin adjusted to the risk group. Group 1 received ceftriaxone, groups 2, 3 and 4 received a broad-spectrum penicillin. We also adapted our empirical therapy to prior identified gum or gut bacterial colonisation and history of MDRB. If an infection was found, antibiotic therapy was secondarily tailored to the identified germ. Vancomycin was stopped after 48 hours if the multiple blood cultures did not identify a Gram-positive-cocci. The aminoglycoside was stopped after 3 injections in the absence of bacterial documentation, and single kidney patients received a single shot.

Statistical analysis

Descriptive statistics were reported in terms of absolute frequencies and percentages. Distribution of data was described in terms of a median or mean value. Simple linear regression and Pearson's correlation tests were used to compare the relationship between different variables. P values <0.05 were considered significant.

RESULTS:

Patients' characteristics

There was a total of 7301 stays in our 2 units from January 2014 to December 2017, with an annual increase. During these 7301 hospitalisations (> to 1 day), we identified 310 BSI among 186 patients; corresponding to a ratio of 4.2% of stays. BSIs accounted for 37.5% to 44% of the center's hospitalisations for fever and febrile neutropenia over these years. Patients with BSIs were aged from 3 days old to 22 years old; 134/310 (43,1%) were females. Patients' characteristics are described in table 1 and suppl. tables 1 and 2.

Bacteria spectrum and risk group distribution (Fig. 1, suppl. fig. 1)

BSIs were mostly observed in groups 1 and 4, with a stable percentage of infections per year in these groups over time. An average of 33,9 % (27,8-36,5%) BSIs in 4 years were recorded in group 1, and 34,1% (27-41%) in group 4. The percentage of BSIs in groups 2, and 3 were respectively 21,6% (13,8-31,7%) and 10,3 % (1,6-15,7%), they were more labile over time (Table 1).

Over the 4 years, among 310 infections, Gram-positive cocci accounted for 72. 9 % of all BSIs: 49.7 % were documented with CoNS with 37.1% of *Staphylococcus epidermidis*, 6.5% with *Staphylococcus aureus* and 3.2% with group D *Streptococcus*. None of the *Staphylococcus aureus* were methicillin resistant. Gram-negative-bacilli accounted for 21.6% of all BSIs, including 14.5% enterobacteria (*Escherichia coli* 14/45 (31.1%); *Enterobacter cloacae* 11/45 (24.4%); *Klebsielle pneumoniae* 8/45 (17.8%)) and 4.5% *Pseudomonas* BSIs. The analysis of the bacterial spectrum according to the groups was not statistically significant. However, we observed around 50% BSIs caused by CoNS in groups 1 and 4. The percentage

of BSIs due to enterobacteria was also the highest in these two groups, respectively 15.6% and 23%. (Fig. 2).

Incidence

The incidence of BSIs dropped over time: 5.5% of annual stay in 2014 and 3.2% in 2017, thus an annual decrease of 0.75% (p=0.002) (Table 1). This statistically significant effect is the resultant of the annual decrease of staphylococcal infections with a drop of 4.4 (p=0.001) BSIs per year. Streptococcal and enterobacteria infections also declined over time, with respectively an annual decrease of 1.8 (p = 0.077) and 3.2 (p = 0.09). Incidence of *Pseudomonas* related BSIs were stable over time.

Reinfections

Our patients had different types of CVADs: 78 central ports, 20 PICCs and 212 tunneled catheters. CVAD were considered as clinical infected in 30 cases (9.7%), and 60 CVAD (19.4%) were removed.

Fifty-eight patients (31%) suffered from a second or more BSI. Thirty-nine patients underwent 2 BSIs, 19 patients underwent 3 BSIs or more BSIs. Fifteen (26.3%) patients were in group 1, and 25 (40.9%) in group 4. There was no statistical difference between the groups (Fig. 3) Among these 58 re-infected patients, 25 had their CVAD removed once and 3 had their CVAD removed twice. Among the patients infected twice, 15/39 patients were re-infected by *Staphylococcus* (CoNS and *Staphylococcus aureus*). Twenty-four patients were re-infected by a different pathogen.

Polymicrobial infections:

We identified 26 episodes of polybacterial infections: 2, or more, identified bacteria in separate blood cultures during the same infectious episode. They occurred in 23 (12.4%) patients, 10 patients were in group 1, 6 in group 2, and 7 in group 4. Three patients suffered from 2 polybacterial BSIs (group 1 and 4). We did not observe a statistical significance between the risk group and the occurrence of polybacterial infections.

Multiresistance, gum and gut colonisation:

Gum and/or gut MDRB colonisation was identified in 65 patients, mostly in group 4 (39/65). Six out of these 65 MDRB were identified as extensively drug resistant bacteria (non-susceptibility to at least one agent in all but two or fewer antimicrobial categories) (17). One child in group 1 had been previously treated in Romania and was colonised with a *Klebsiella pneumoniae* producing carbapenemase (OXA 48) and an *Enterococcus faecium* resistant to glycopeptides. Three other children, treated in our center only were colonised with 2 *Enterobacter cloacae*, 2 *Klebsielle pneumoniae*.

Eleven BSIs (3.5%) were identified as MDRB: 5 *E.coli*, 3 *Klebsiella pneumoniae*, 1 *Enterobacter cloacae*, 1 *Klebsielle oxytoca*, 1 *Hafnia alvei*. Eight of these MDRB infections were primo-infections. One patient had originally been treated in eastern Europe and was colonised with MDRB at his arrival. Three MDRB infections were caused by reinfections. Six of them were associated with a gum or gut bacteria translocation, 3 in group 1, 1 in group 2 and 2 in group 4. All gram-positive bacteria were susceptible to vancomycin. We report no extensively drug resistant bacteria in BSIs.

DISCUSSION:

Immunocompromised children, due to malignancies and their treatments or caused by primary immunodeficiency, encounter a high risk of BSIs. BSIs are the most frequent complications and causes of hospitalisation in this specific population. The epidemiology of bacteria causing BSIs has shifted from Gram-Negative organisms in the 1970s to Gram-Positive organisms over the last years (4). Furthermore, the rapid development and the global spread of multidrug resistant bacteria is a major health care issue worldwide. Knowledge of pathogens distribution and resistance patterns is paramount for an optimal empiric antibiotic therapy and outpatient management.

In this study, we examined the spectrum and resistance profile of bloodstream infections in pediatric immunocompromised patients in relation to their immunosuppression level. In our center the incidence of BSI dropped over time 4.3 % (3.2-5.5%). The majority of BSIs (72.9 %) were caused by Gram-positive cocci, particularly CoNS. Among the Gram-negative bacteria, enterobacteriae were the most common ones. These results are coherent with worldwide experience of BSI in pediatric hematology and oncology (18). Opportunistic infections caused by Gram-positive bacteria among our population may be the product of several cofactors including neutropenia, intensive chemotherapy, presence of invasive devices such as CVADs, and mucositis. In accordance to Miedema et al (1) we did not identify a single case of BSIs due to methicillin resistant *Staphylococcus aureus* or vancomycin-resistant enterococci. We report no extensively drug resistant enterobacteria. These results are also consistent with European studies performed in pediatric oncology treatment centers in Germany, Switzerland and the Netherlands (19) where the proportion of MDRB-related BSIs remained consistently low (1,5% of all BSIs). Bacterial spectrum in the current study was comparable to the one observed in non-hemato-oncological pediatric centers such as intensive care unit, neonatology (20). Our protocol was thus well adapted to the local ecology:

vancomycin targeted CoNS whereas Gram-negative bacteria were controlled by a broad-spectrum penicillin. An aminoglycoside was added for the synergic effect.

Our protocol diverges from the 2012 guidelines for management of febrile neutropenia in children with cancer and/or undergoing HSCT (21). Indeed, these guidelines strongly recommend monotherapy as first line treatment, with an antipseudomonal β-lactam or carbapenem as empiric therapy in the high-risk group. A second anti Gram-negative agent or a glycopeptide was added only for clinically unstable patients. We agree with the overall goal: minimising exposure to avoidable antibiotics while providing coverage for virulent organisms. An excessive use of broad-spectrum antibiotics may accelerate resistance rates. However, with our step-down strategy, we were able to rapidly stop unnecessary antibiotics at 48h. Moreover, initial broad-spectrum multiple therapy enabled a rapid control of BSIs: the early use of glycopeptides allowed a rapid control of more than 50% of our BSI and does not appear to trigger vancomycin resistant CoNS. *Pseudomonas* is responsible for a minority of our BSI whereas enterobacteria represents the most common Gram-negative bacteria. We then prefer to reserve carbapenem for documented penicillin resistant germs and MDRB, and thus avoid selection of new resistant bacteria. The lack of resistance of our Gram-negative isolates is reassuring and reflects the tight regulation of broad-spectrum antibiotics in our unit. There are major limits to our study which is a retrospective evaluation over a short period of time, in a single center. We could consider, in order to diminish antibiotic exposure, to restrain the use of aminoglycosides. They would be used in case of severe sepsis or in patients with a high risk of BSI caused by digestive pathogens. This would then be individually discussed and re-evaluated over time.

Thanks to our antibiotic protocol, the early administration of intravenous antibiotics enabled a quick control of the BSIs. The step-down therapy at 48h depended on clinical and

biological features. The patients with a controlled CoNS BSIs (apyrexia, benign clinical features, sterilisation of blood cultures, vancomycin adapted concentration levels (22)) could be discharged within 72 hours and the treatment was pursued at home with the outpatient hospitalisation. This early outpatient management strategy considerably increased the children's quality of life. With a rapid control of the infection we were also able to sterilise 81% of CVAD without the use of an antibiotic lock. For thirty-three patients we controlled the BSIs without adding the burden of another intervention. The 25 remaining patients had a second surgery to replace the CVAD. These results are meaningful: changing a CVAD is a non-negligible intervention in terms of morbidity and the health costs. This outcome highlights the importance of medical and parental education: a key point in the primary prevention of BSIs. The nurses as well as the parents followed strict aseptic rules regarding the use and manipulation of the CVAD. Furthermore, our unit has set up a training program for the nurses over the last years.

To our knowledge this is the first study that analyses the microbiological spectrum of bacteria related BSIs in immunocompromised children, with risk stratification on the level of immunosuppression. A strength of this study is that we are unique: we treat in the same institute blood cancers, solid tumors, benign platelet and red blood cell pathologies, congenital immunodeficiency and we perform HSCT. The diversity of the diseases we treat gives legitimacy to the study, even if monocentric.

Our study reveals the same number of documented BSIs in the highest immunosuppression group (group 4) than in the less immunocompromised group (group 1). This last group could be compared to children treated by immunosuppressive treatments on the long term. In adult oncology units, a cohort which can be compared to our group 1, febrile neutropenia are treated

with oral antibiotics. The 2012 guidelines for the management of pediatric febrile neutropenia(21) also recommend (weakly, 2B) oral antibiotic administration in children with low risk febrile neutropenia. Our present study demonstrates a high proportion of BSIs caused by *Staphylococcus* (50%) and enterobacteria (15%) in this low risk group. Such pathogens, in association with a CVAD, cannot be treated with oral medication only (21). Additionally, oral antibiotics encounter major difficulties in children compared to parenteral antibiotics: drug form, palatability, cooperation of younger children, impaired gastrointestinal absorption, mucositis. These results stress the importance of a close follow up during the entire treatment in all risk groups.

Reinfections were a major issue in our study: 31% patients suffered from a reinfection. Interestingly their immunocompromised status was not correlated to a higher risk of reinfection as we could have supposed. The patients were predominantly reinfected by different pathogens and were not more likely to have MDRB. We did not identify the sources of all reinfections. It could be interesting to study the different risk factors of reinfections. They are a true burden for the families and the patients who are re-hospitalised in most cases. Survival rates now exceed 70% in child cancer however reducing the morbidity is tomorrow's challenge.

A decontamination was performed in our center in the highest immunocompromised groups 3 and 4. However, prophylactic administration of oral antibiotics stays a debated issue. By modulating the composition of the hosts' intestinal microbiota to prevent infections, decontamination damage the gut epithelial barrier. Murine studies suggest that metabolites generated by the gut microbiota not only regulate intestinal immune homeostasis, but also influence circulating immune cells (23). A recent study revealed the occurrence of a higher rate of acute graft-versus-host disease after HSCT in patients who received gut decontamination.

The authors suggested that microbiota alteration could participate in a systemic pro-inflammatory response and alter intestinal immune homeostasis (22). One must also consider that the gut microbiota can be altered by other cofactors during these infectious episodes such as fasting, mucositis, parenteral nutrition. The major limit to gut and gum decontamination is non-observance, especially in teenage patients (24). Indeed, an incomplete decontamination will inevitably select resistant bacteria. Interestingly, in our study, we observed only 6 BSI (9.2% of the 65-positive gut/gum samples) caused by a bacterial agent identified in both blood culture and gut/gum sample. However, this number is probably underestimated, the sensitivity of bacterial identification through gum and gut sample remains low. Prospective studies that evaluate the contribution of bacterial decontamination to the emergence of MDRB are needed.

CONCLUSION:

BSI in immunocompromised children are mainly caused by Gram-positive bacteria, this result is consistent with worldwide experience. In our center, the incidence of BSIs declined over the 4 years due to a decrease of staphylococcal infections. This result stresses the importance of medical and parental education concerning the management of CVADs. The low and constant number of MDRB related BSIs is encouraging. The short use of vancomycin does not trigger the emergence of resistant bacteria. Regarding the immunosuppression levels we must stay alert, BSIs remain a major cause of morbidity even in the less immunosuppressed patients. A prospective multicenter study involving pediatric oncology and hematology units is required to address the limitations identified by this study.

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Table 1: BSIs per year and per level of immunosuppression

		2014	2015	2016	2017	4 years
	Hospitalisations	1633	1735	1948	1985	7301
	BSI (%)	89 (5,5%)	80 (4,6%)	78 (4,0%)	63 (3,2%)	310 (4,2%)
Group 1	Total	32 (36%)	29 (36,3%)	21 (27,8%)	23 (36,5%)	105 (33,9%)
Solid tumors	Age (y) (median-range)	2,9 (0,1-20,2)	2,4 (0,3-19,2)	2,6 (0,8-18,3)	3,7 (0,5-22,1)	
Hodgkin Malignant Lymphoma	CVAD local infection	4 (4,5%)	4 (5%)	1 (1,3%)	1 (1,6%)	10 (3,2%)
	CVAD removal	9 (10,1%)	9 (11,3%)	4 (5,1%)	6 (9,5%)	28 (9%)
	MDRB septicemia	2 (2,2%)	1 (1,3%)	0	2 (3,2%)	5 (1,6%)
	MDRB identified translocation	0	1 (1,3%)	0	2 (3,2%)	3 (1%)
	Gum and gut MDRB colonisation	1 (1,1%)	0	0	7 (11,1%)	8 (2,6%)
Group 2	Total	19 (21,3%)	11 (13,8%)	17 (21,8%)	20 (31,7%)	67 (21,6%)
ALL: Low and medium risk groups	Age (y) (median-range)	4,7 (1,2-16,3)	2,8 (0,3-8,5)	4,1 (1,4-13)	3,8 (1,7-16,5)	
Non Hodgkin Malignant lymphoma	CVAD local infection	1 (1,1%)	1 (1,3%)	0	3 (4,8%)	5 (1,6%)
Metastatic neuroblastoma	CVAD removal	4 (4,5%)	4 (5%)	5 (6,4%)	5 (7,9%)	18 (5,8%)
	MDRB septicemia	1 (1,1%)	0	1 (1,3%)	0	2 (0,6%)
	MDRB identified translocation	1 (1,1%)	0	0	0	1 (0,3%)
	Gum and gut MDRB colonisation	4 (4,5%)	2 (2,5%)	0	10 (15,9%)	16 (5,2%)
Group 3	Total	14 (15,7%)	9 (11,3%)	8 (10,1%)	1 (1,6%)	32 (10,3%)
ALL: High risk group	Age (y) (median-range)	3,4 (1,3-15,9)	15,2 (0,5-17,9)	11,1 (4,2-19,5)	1,2	
High risk Burkitt lymphoma / leukemia	CVAD local infection	0	2 (2,5%)	0	1 (1,6%)	3 (1%)
Non Hodgkin Malignant lymphoma high risk group / relapse	CVAD removal	1 (1,1%)	1 (1,3%)	1 (1,3%)	0	3 (1%)
	MDRB septicemia	2 (2,2%)	0	0	0	2 (0,6%)
	MDRB identified translocation	0	0	0	0	0
	Gum and gut MDRB colonisation	4 (4,5%)	1	0	0	5 (1,6%)
Group 4	Total	24 (27%)	31 (38,8%)	32 (41%)	19 (30,2%)	106 (34,1%)
AML	Age (y) (median-range)	5,3 (0,6-18,6)	7,4 (1,3-20,9)	3,0 (0,4-18,7)	11,8 (0,9-18,7)	
Acute Leukemia relapse	HSCT	12 (13,5%)	11 (13,8%)	22 (28,2%)	13 (20,6%)	58 (18,7%)
Medullary aplasia	CVAD local infection	1 (1,1%)	0	10 (12,8%)	1 (1,6%)	12 (3,9%)
Severe combined immunodeficiency syndrome (SCID)	CVAD removal	2 (2,2%)	2 (2,5%)	5 (6,4%)	2 (3,2%)	11 (3,5%)
HSCT (allogenic, autologous)	MDRB septicemia	1 (1,1%)	0	2 (2,6%)	1 (1,6%)	4 (1,3%)
	MDRB identified translocation	1 (1,1%)	0	1 (1,3%)	0	2 (0,6%)
	Gum and gut MDRB colonisation	7 (7,9%)	12 (15%)	16 (20,5%)	4 (6,3%)	39 (12,6%)

ALL: Acute lymphoblastic leukemia
AML: Acute myeloid leukemia
HSCT: Hematopoietic stem cell transplantation
MDRB: Multi-drug resistant bacteria

Figure 1: Bacterial spectrum per year

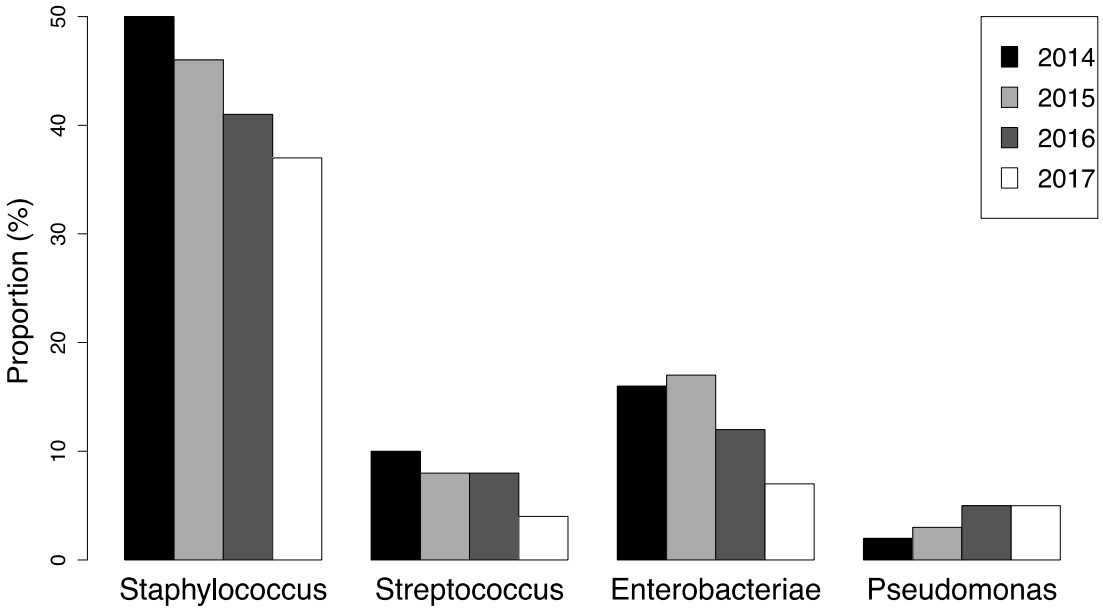


Figure 2: Bacteria causing BSIs per group

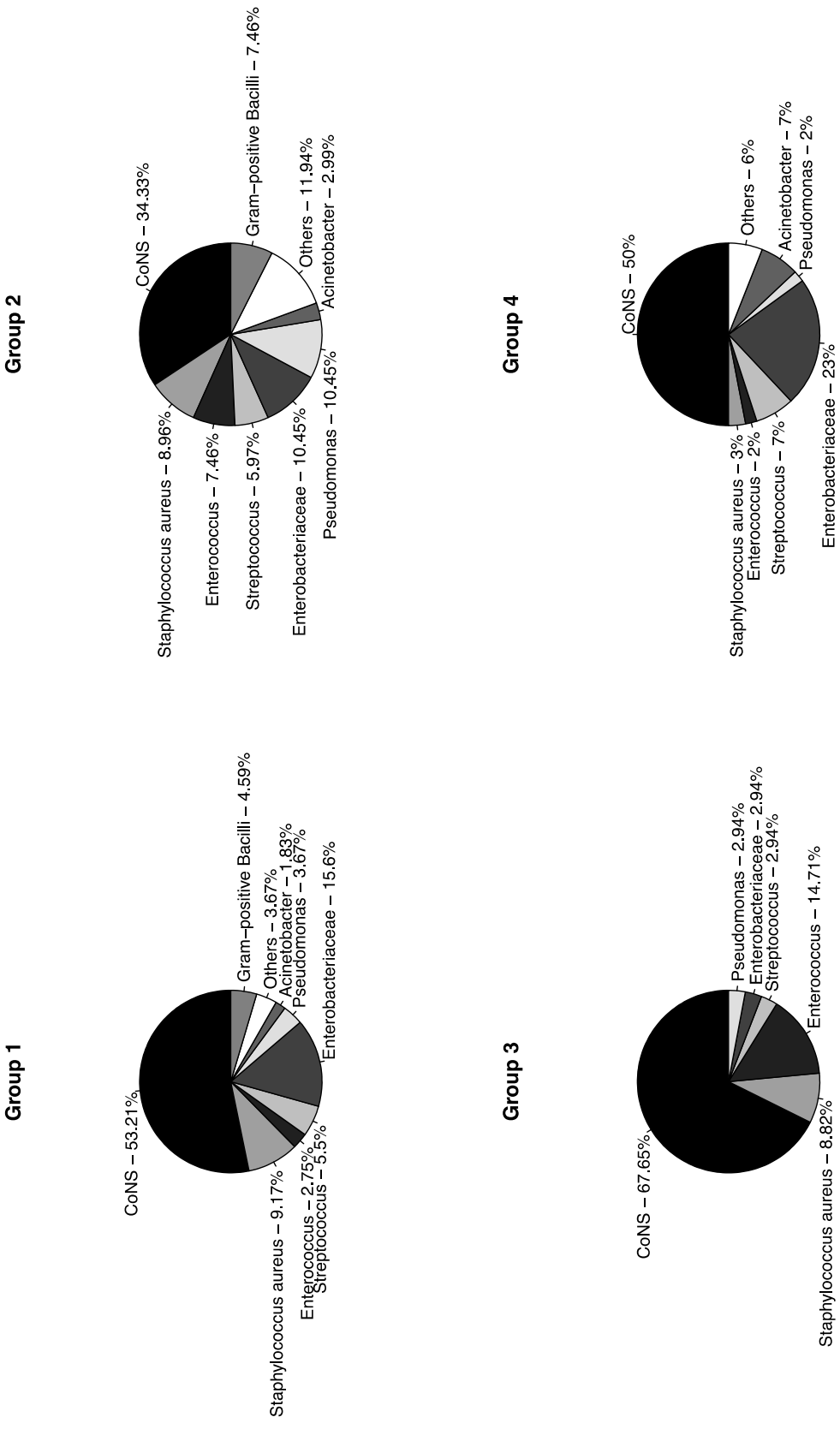
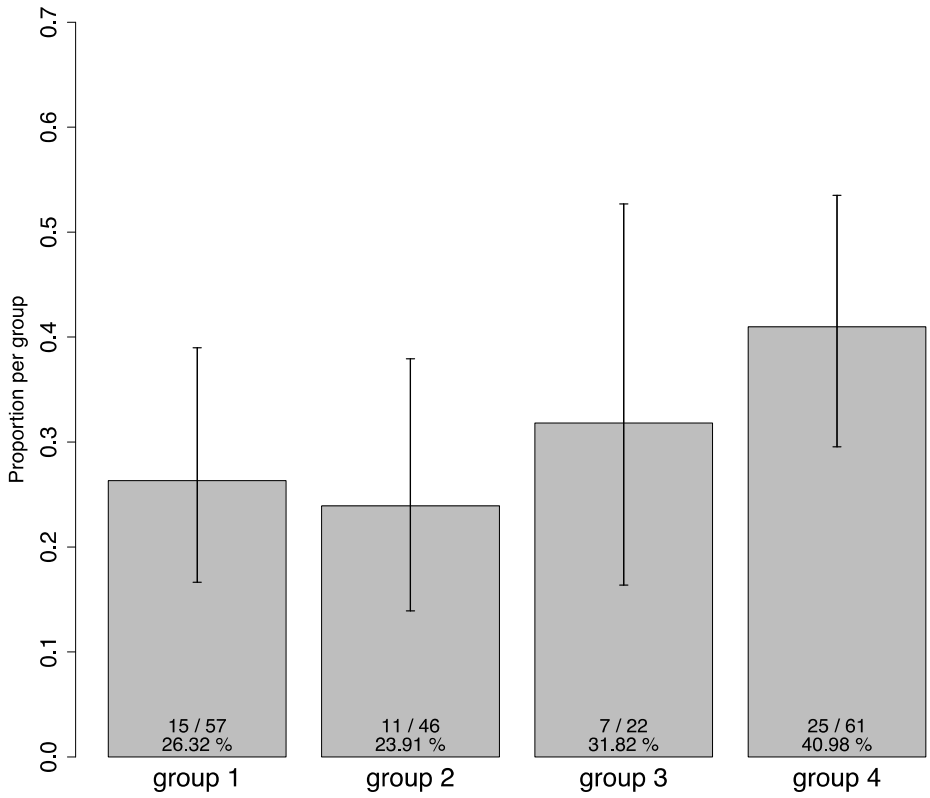
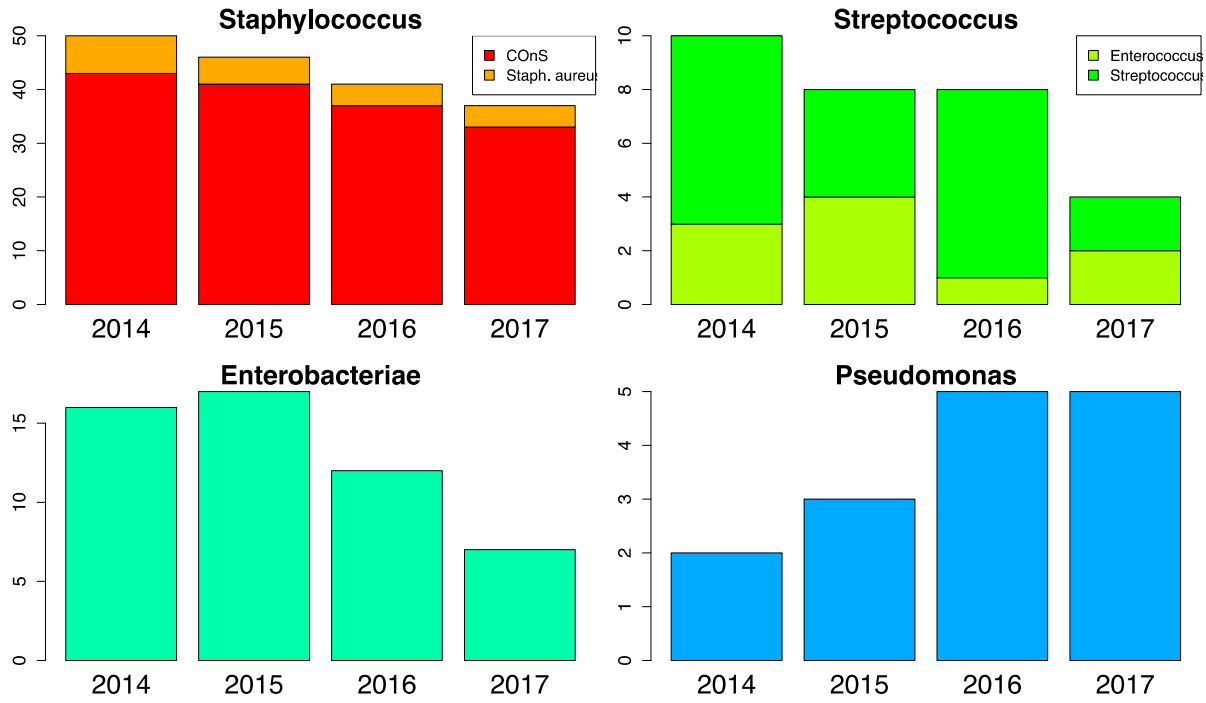


Figure 3: Number of reinfections per risk group



Supplemental figure 1: Detailed bacterial spectrum per year



Supplemental table 1: BSIs per year and disease, patients' characteristics

	2014	2015	2016	2017	4 years
Total BSI	**89**	**80**	**78**	**63**	**310 (%)**
Pre/post HSCT for non tumoral pathologies					
Benign red cell and platelet pathology	3	1	1	2	7 (2,3)
Bone marrow failure	4	2	7	1	14 (4,5)
Congenital immunodeficiency	5	4	3	3	15 (4,8)
Other (adrenoleukodystrophy)	1	0	0	0	1 (0,3)
Leukemias					
ALL in first line	25	17	19	18	79 (25,5)
* Low risk ALL	1	5	4	3	13 (4,2)
* Medium risk ALL	9	1	9	13	32 (10,3)
* High risk ALL	15	11	6	2	34 (11)
AML in first line	4	8	6	3	21 (6,8)
JMML	0	2	9	0	11 (3,5)
Relapses	6	12	7	8	33 (10,6)
Non-Hodgkin Malignant Lymphoma	0	6	3	2	11 (3,5)
Solid tumors					
Sarcoma	15	4	12	10	41 (13,2)
Cerebral tumors	7	5	3	10	25 (8,1)
Metastatic neuroblastoma	10	5	4	2	21 (6,8)
Others	9	13	3	2	27 (8,7)
Palliative care	0	1	1	2	4 (1,3)

ALL: acute lymphoblastic leukemia
AML: acute myeloblastic leukemia
BSI: bloodstream infection
HSCT: hematopoietic stem cell transplantation
JMML: juvenile myelomonocytic leukemia
Sarcoma (osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, undifferenciated sarcoma)

Supplemental table 2: Features of patients who underwent allogeneic stem cell transplantation

			Stem Cell Sources			HLA-compatibility	
Underlying disease	**Total of patients**	**Total of BSI**	**Bone marrow**	**Peripheral blood**	**Cord blood units**	**geno-identical**	**pheno-identical**
Acute leukemia (High risk, relapse)	20	24	14	1	5	5	15
Adrenoleukodystrophy	1	1	1	0	0	0	1
Beta Thalassemia major	1	1	1	0	0	0	1
Chronic myeloid leukemia	1	1	1	0	0	1	0
Chronic septic granulomatosis	1	1	1	0	0	0	1
Juvenile myelomonocytic leukemia	1	9	1	0	0	1	0
Medullary aplasia	3	9	2	1	0	0	3
SCID	3	7	1	0	2	0	3
Sickle cell anemia	2	2	2	0	0	2	0
Wiskott-Aldrich syndrome	1	2	0	0	1	0	1
XIAP deficiency	1	2	1	0	0	0	1

BSI: bloodstream infection
SCID: severe combined immunodeficiency

7. Conclusion en français

En conclusion, notre étude corrobore les données européennes actuelles : les bactériémies chez l'enfant immunodéprimé sont majoritairement causées par des Cocci Gram-Positifs. De plus, nous avons observé entre 2014 et 2017 une décroissance de l'incidence des bactériémies principalement attribuable à la diminution des infections systémiques à staphylocoque.

Nous rapportons au travers de cette étude qu'un très faible et constant nombre de bactériémies sont causées par des bactéries multirésistantes. L'utilisation courte et raisonnée de vancomycine n'a pas induit, à notre connaissance, de résistance bactérienne. Notre antibiothérapie probabiliste large spectre ne semble pas avoir été associée à l'émergence de bactéries multirésistantes.

Par ailleurs, cette étude regroupant tous les niveaux d'immunodépression de l'enfant, nous alerte sur l'importance de rester vigilant : tout enfant immunodéprimé, et ce quel que soit son statut d'immunosuppression, est à risque de bactériémie

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.
J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.
Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.
Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.
Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés.
Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.
Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.
Je ne provoquerai jamais la mort délibérément.
Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.
Que je sois modéré en tout, mais insatiable de mon amour de la science.
Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.
Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,
Que je sois déshonoré et méprisé si j'y manque.

RAAD Coralie (née HARDY)

SUJET DE LA THESE:
Bloodstream infections in immunocompromised children and emergence of multi-resistant bacteria

THESE: MEDECINE
Qualification: Médecine Spécialisée en pédiatrie
ANNEE: 2019

NUMERO D'IDENTIFICATION : 2019ANTI0465

MOTS CLEFS : bactériémies – immunodépression – cancer pédiatrique - antibiothérapie – bactéries multirésistantes

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RESUME DE LA THESE

L'objectif principal de ce travail a été d'étudier l'épidémiologie des bactériémies chez les enfants immunodéprimés : identifier le spectre bactérien ainsi que la résistance bactérienne aux antibiotiques. Il s'agissait d'une étude descriptive et rétrospective menée de janvier 2014 à décembre 2017 à l'institut d'hématologie et d'oncologie pédiatrique de Lyon. 310 (4.2%) bactériémies furent identifiées chez 186 patients. Les Cocci Gram-Positifs étaient majoritaires, (72,9 %). L'incidence annuelle des bactériémies diminua de 0.75% (p =0.002) par an. Seules 3.5% des bactériémies furent causés par des bactéries multirésistantes. Chez nos patients immunodéprimés, les bactériémies documentées ont majoritairement été attribuées à des Cocci-Gram-Positifs. Dans cette étude, l'utilisation raisonnée d'antibiotiques à large spectre n'a pas été associée à l'émergence de bactéries multirésistantes.

JURY : Président: Pr Narcisse ELENGA
Juges : Pr Yves BERTRAND
: Pr Yves GILLET
: Dr HALFON DOMENECH
