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Adherence to preventive measures after splenectomy in the hospital setting and in the community

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Summary Overwhelming post-splenectomy infection (OPSI) remains a long-term risk in asplenic patients, which may be reduced by appropriate preventive measures. Specific guidelines have been developed to lower its incidence.
Aims: To assess the implementation of guidelines by specialized physicians of a university hospital and primary care physicians.
Methods: A retrospective review of splenectomized patients' medical files over a six year period was carried out. Patients' general practitioners were contacted and a questionnaire was sent to them.
Results: 154 individuals who underwent splenectomy between 2000 and 2005 were eligible (62 children and 92 adults): 70.8% received vaccine, 44% received

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pneumococcal vaccine against *Haemophilus influenzae* type b with a good cover of children population (88.7%), 24% received meningococcal vaccine. Prophylactic antibiotics were prescribed in 74% of patients. Septic events were found in 8.4%, and global mortality was 11.7% during a mean follow-up period of 4.5 years.
Conclusions: Management of the infectious risk in asplenic patient has to be improved: some of the patients are not correctly identified as at risk of OPSI, and vaccination against *Neisseria meningitidis* is insufficient. Hospital specialists should improve the implementation of guidelines and give better information to general practitioners involved.
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Introduction

Individuals with anatomical or functional asplenia are known to be at increased risk of severe and potentially life-threatening infections [1]. Furthermore, multiple reviews have documented that despite the implementation of education, prescription of prophylactic antibiotics and vaccination against encapsulated bacteria are far from systematic [2]. It has been estimated that there are 500,000 asplenic patients in France [3] of whom 50% are splenectomized, while the remaining patients have functional hyposplenism (mostly severe liver disease, celiac sprue, but also sickle-cell disease, thalassemia, autoimmune or granulomatous diseases).

These patients have a considerable risk of developing invasive infections, such as meningitis or bacteremia. These infections are called overwhelming post splenectomy infections (OPSI) and were identified in 1952 [4]. Their major characteristics are a high mortality rate (up to 70% within 48 h in a review of the literature on post-splenectomy sepsis from 1952 to 1987 [5]), a minor and short prodromic phase, and a high bacteremia or parasitemia. Pathogens most often involved are encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis* or intra-erythrocytic parasites or bacteria where elimination is mostly splenic (*Babesia* spp., *Ehrlichia* spp., *Plasmodium* spp.) [6]. *S. pneumoniae* is the first agent involved in OPSI, followed by *H. influenzae* type b in children [7].

The risk for asplenic patients to develop an OPSI is estimated to be 0.89% per person per year [8].

Several recommendations and guidelines exist in the literature, the most recent being published in 2010 in Australia [9], the United States in 2006, and Great Britain in 2008 [10—13]. These recommendations are based on three principles: immunization against *S. pneumoniae, N. meningitidis, H. influenzae* type b, and influenza, lifelong antibiotic prophylaxis, and education with written information and cards to alert health professionals, and risks associated with travels or animal bites. Despite these recommendations and efforts to implement them, the incidence of OPSI remains constant over time, ranging from 4.25% in 1973 [14] to 3.2% in 2001 [15].

The mortality of OPSI and the high number of cases of OPSI in young patients without comorbidity brings into question the compliance and efficacy of these preventive measures. Because the adherence to preventive measures is critical to their success and is reported to be low while the mortality of OPSI remains high, a retrospective study was conducted to assess the vaccination status and antibiotic prophylaxis in splenectomized adults and children during a 6-year period in the Paris Descartes University hospitals. It was also investigated whether the general practitioners in charge of the patients were up-to-date with recommendations.

Methods

A retrospective study was carried out in the Paris Descartes University hospitals. Three major hospitals were included (Necker, Cochin and Pompidou). These three hospitals, with a total of 2600 beds, cover various specialities: paediatric haematology and immunology, adult and paediatric general surgery, adult haematology, gastroenterology, gynaecology, infectious and tropical diseases and internal medicine.

Table 1 Demographic data, underlying diseases and outcome of 154 splenectomized patients.

	All patients	Adults	Children
Number of patients	154	92 (60)	62 (40)
Age at splenectomy (years)	36.8 ± 27.6	56.2 ± 17.8	8 ± 5.0
Indication of splenectomy			
Haemolytic anemia[a]	33 (21)	9 (10)	24 (39)
Idiopathic thrombocytopenia	32 (20)	17 (18)	15 (24)
Trauma/iatrogenic	26 (17)	25 (27)	1 (2)
Hematological malignancy	26 (17)	22 (24)	4 (6)
Hemoglobinopathy (sickle cell disease and thalassemia)	10 (6)	1 (1)	9 (15)
Others	31 (20)	22 (24)	9 (15)
Comorbidities			
Evolutive neoplasia	38 (25)	36 (39)	2 (3)
Immunosuppressive treatment[b]	24 (16)	11 (12)	13 (21)
Immune deficiency[c]	7 (5)	1 (1)	6 (10)
Diabetes mellitus	4 (3)	4 (4)	0 (0)
HIV infection	2 (1)	1 (1)	1 (2)
Invasive infections	13 (8.4)	9 (10)	4 (6)
Global mortality	18 (12)	15 (16)	3 (5)

Data is expressed as mean ± standard deviation or number (percentage).

[a] Excepting hemoglobinopathy.

[b] Immunosuppressive treatment consisted in: steroid therapy, antineoplasic treatment (chloraminophene, fludarabine, rituximab, cyclophosphamide, cladribine, cytarabine), infliximab treatment, anti rejection treatment (mycophenolate, ciclosporin).

[c] Immune deficiency consisted in: Fas-ligand deficiency, Wiskott Aldrich syndrome, severe combined immune deficiency, Canale-Smith syndrome, Evans syndrome, bone marrow transplantation, liver cirrhosis.

Patients who underwent splenectomy from 1 January 2000 to 31 December 2005 were identified using the database of pathology departments in the three participating hospitals. Criteria of exclusion were the unavailability of medical charts and death during or within the first 48 h following splenectomy.

Data were first collected from these different medical units and demographic and clinical data were reviewed extensively: they included the age, the indication of splenectomy, co-morbidities, vaccination status and timing, antibiotic prophylaxis, antibiotics used at home in case of fever, and information which had been given to patients or relatives. All infectious events requiring hospitalization and their characteristics were also studied during a follow-up of at least two years after splenectomy.

Last, the patients' general practitioners (GP) were questioned. They were contacted by telephone and sent a standardized questionnaire including details of antibiotic prescription, immunization against *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, influenza virus and information delivered to the patients. 77 GPs were contacted, of whom 46 were still following patients selected in the study and answered the questionnaire.

An univariate analysis was used to assess predictive factors of failure for preventing OPSI. Statistics tests used were Chi2 Pearson test and Fischer's test. Statistical analyses were performed using SPSS software version 12 (SPSS Inc., Chicago, Ill). All statistical analyses were performed using 2-tailed tests, with significance at $p < 0.05$.

Results

General characteristics

195 patients underwent splenectomy during the study period. 34 medical charts were lost, and 7 deaths occurred during surgery or within the first 48 h. A total of 154 charts were thus reviewed. Demographic characteristics, comorbidities, and indications for splenectomy are presented in Table 1. Indications for splenectomy mainly consisted in haemolytic anemia in children (39% versus 10% in adults, $p < 0.0001$). Underlying diseases were mainly hereditary spherocytosis and autoimmune haemolytic anemia. Hematological malignancies and solid tumors were the leading indications for splenectomy in adults (38% in adults versus 7% in children, $p = 0.0034$) (Fig. 1).

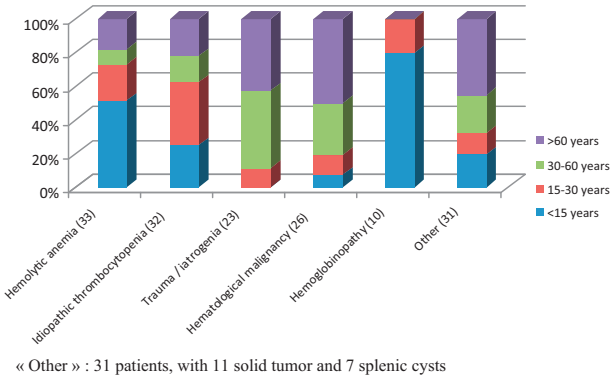

Figure 1 Age repartition for indications of splenectomy. Other: 31 patients, with 11 solid tumor and 7 splenic cysts.

Global mortality during follow-up was 11.7% (18 patients).

Adherence to preventive measures in hospital (Table 2)

S. pneumoniae

75 pneumococcal vaccinations were performed before surgery over 128 programmed procedures (vaccine before surgery of 58.6%). 34 vaccinations were administrated after surgery.

H. influenzae type b

All children born after 1992 ($n = 38$) received vaccination, as recommended since 1992 in France. 29 other patients (15/92 adults and 14/62 children) were immunized before surgery and 22 after (20/92 adults and 2/62 children).

N. meningitidis

31 meningococcal vaccinations were administered before surgery (5/92 adults: 19-, 19-, 23-, 36-, and 67-year old and 26/62 children) and 6 after surgical intervention (2 adults and 4 children). Many serotypes were used: A, A-C, A-C-Y-W135.

Vaccination against influenza virus was reported in only two medical charts, corresponding to a cover of 1.3%.

Table 2 Immunizations coverage and antibiotic prophylaxis among children and adults populations at hospital discharge.

	Children = 62	Adults = 92
Streptococcus pneumoniae	65%	75%
Haemophilus influenzae type b	89%	37%
Neisseria meningitidis	45%	10%
All the 3 recommended vaccines	40%	4%
No immunization	23%	35%
Antibioprophylaxis	90%	64%

All vaccinations or none

29 patients received all recommended immunizations (18.8%). Among these patients, half of them were splenectomized for haemolytic anemia (49%) and a fourth for idiopathic thrombocytopenia (24%), as presented in Fig. 3. 46 patients (29.9%) did not receive any vaccination after hospital discharge; indications of their splenectomy are presented in Fig. 4 (mostly represented by splenectomy for solid tumor and for trauma).

Antibiotic prophylaxis

107 patients received oral penicillin, 7 patients received another antibiotic: amoxicillin (3), roxithromycin (1), benzathine benzylpenicillin (1), norfloxacin (1), and spiramycin (1). A total of 74.0% of the population received an antibioprophylaxis: 90% of children and 64% adults. The duration of antibioprophylaxis was not reported, but when it had been prescribed, no GP had stopped it.

General practitioner's attitudes

Among 46 patients still followed by a GP, 8 outpatients were never immunized against pneumococcal infection: the pneumococcal vaccine by general practitioner (GP) was 82.6%. Only 2 of these 46 patients did not receive any antibioprophylaxis.

20 patients were vaccinated against influenza virus at least once during the follow-up period (of 43.5%).

Factors linked to pneumococcal vaccination by GP were analysed. They are presented in Table 3. There was a good knowledge of infectious risk in patients under immunosuppressive therapy and patients splenectomized for idiopathic thrombocytopenia. This contrasted with patients splenectomized for trauma or hemoglobinopathy which were not identified as at risk.

Finally, the differences between the practices of the GP and hospital physicians are presented in Table 4: pneumococcal vaccine was equivalent in the two groups and so was antibioprophylaxis, but information given to patients differed, with 19.5% of patients informed at hospital and 62.5% by their GP.

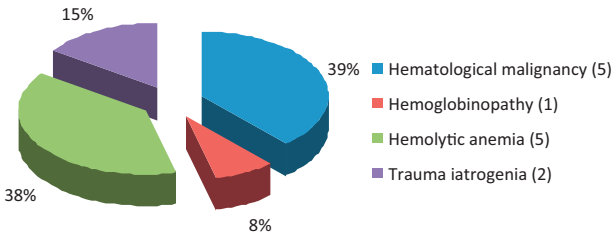

Figure 2 Indication for splenectomy among 13 patients who presented a subsequent infection.

Description of infections requiring a hospitalization

13 patients (8.4%) including 6% of children and 10% of adults, after a mean interval of 16 months following splenectomy, developed an infection requiring hospitalization, with a mortality rate in this group of 23.1%. Inversely, mortality due to infections in this study is 4 deaths among 18, corresponding to 22.2%. The clinical characteristics of these infections consisted of six episodes of pneumonia, five bacteremia, and two pyelonephritis. The identified pathogens (9 out of 13 events) were: *Escherichia coli* in three cases, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, one pneumonia for which several pathogens were isolated including *Streptococcus mitis, Neisseria sicca,* and *Staphylococcus aureus*, one *Pneumocystis jiroveci*, one *Stenotrophomonas maltophilia*, and one acute episode of malaria due to *Plasmodium falciparum*. These 13 patients had a pneumococcal-vaccination cover of 92.3%, haemophilus-vaccination cover of 92.3%, meningococcal-vaccination cover of 15.4%, and they received antibiotic prophylaxis in 69.3% of cases. Indications of splenectomy among patients who presented an OPSI are presented in Fig. 2.

Discussion

The aim of the study was to determine how hospital physicians and general practitioners followed

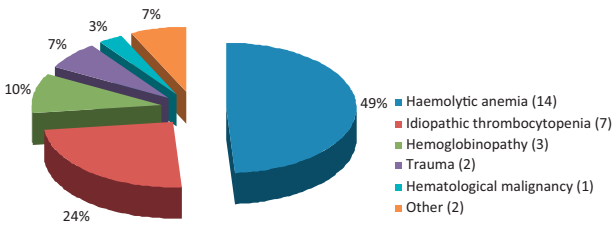

Figure 3 Indications for splenectomy in fully immunized patients (i.e. having received the 3 recommended vaccines before surgery).

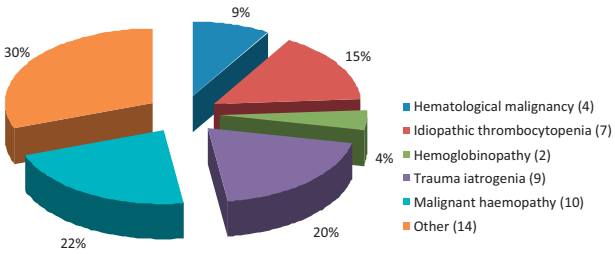

Figure 4 Indications for splenectomy among non-vaccinated patients.

guidelines for prevention of infections in splenectomized patients in Paris.

Concerning immunizations, we observed good vaccine coverage against pneumococcal infection (70.8%), was observed especially for patients who were followed by a GP (82.6%). This rate is in the upper range of that previously reported, which varied from 32% to 75% [16—18]. However, the need for immunization against *H. influenzae* type b and *N. meningitidis* is not well taken into account by hospital physicians, with respectively 44% and 24% of vaccine coverage at hospital discharge. The insufficient coverage for meningococcal and *Haemophilus* vaccinations was found in all recent studies, with similar results in a 2001 study in Canada [19,20,21].

Antibiotic prophylaxis was prescribed to 74% of patients in hospital. However, patients with lower coverage were those who underwent partial splenectomy and splenectomy for solid tumor. Indeed, it is now well known that an infectious risk exists even in patients with a residual spleen—the immune capacity of residual or accessory spleen being not assessable [3,22]. The lack of proper antibiotic prophylaxis in patients with solid tumor can be explained by the fact the infectious risk associated with splenectomy might be perceived as minor when compared with the risk associated with malignancies. In this clinical setting, it is, however, recommended to insist on the use of antibiotics at home in case of fever and on antimicrobial prophylaxis during the period of immunodeficiency. Indeed, those patients are at particularly high risk of infections, since they can also be neutropenic or receive high doses of corticosteroids.

Data regarding advice given to patients and prescription of antibiotics in case of fever occurring at home were difficult to collect in this series. This information is often not reported in clinical charts. Percentage of patients for whom antibiotics were prescribed in case of fever by hospital physicians and GP were respectively 13% and 8.7%. Many studies tried to evaluate patients' knowledge regarding their infectious risk. In order to assess the observance of these prophylaxes, a recent study

Table 3 Vaccination against *Streptococcus pneumoniae* by GPs (after splenectomy).

All patients = 46	Vaccinated = 29 (63)	Non vaccinated = 17 (37)	*p*-Value
Age (years)	37.5 ± 28.7	38 ± 26	NS
Gender	17 men/12 women	8 men/9 women	NS
Hematological malignancies	7 (24)	3 (18)	NS
Hemoglobinopathy	0	**3 (18)**	**<0.005**
Haemolytic anemia	13 (45)	2 (12)	NS
Trauma	0	3 (18)	**<0.0005**
Idiopathic thrombocytopenia	**6 (21)**	0	**<0.006**
Diabetes	1 (4)	1 (6)	NS
Immunosuppressive treatment	**7 (24)**	0	**<0.002**
HIV	1 (4)	1 (6)	NS
Cancer	6 (21)	5 (29)	NS
Immune deficiency	1 (4)	0	NS

Data is expressed as mean ± standard deviation or number (percentage).
NS: no statistically significant difference observed.

evaluated the presence of penicillin in urine of recently splenectomized patients, who were known to have been prescribed oral penicillin: only 42% took it correctly [23]. Similarly, a questionnaire-based study performed months to years after splenectomy, assessed the ''level of knowledge about infectious risk'' and ''good behaviour in case of fever'': all patients were interviewed by a doctor or a nurse before discharge and received a card or bracelet and underwent the 3 classical vaccinations. Nevertheless, only 47% of patients recalled having received good information, and 27% reported a correct behaviour in case of fever [24].

Furthermore, results about missing pneumococcal vaccination by GP could help identifying a high-risk population. It appears that patients splenectomized for hemoglobinopathy (thalassemia and sickle-cell disease) and trauma are indeed under-vaccinated. However, an increase of infection rate in this group was not observed, owing to a potential residual splenic tissue in this context, as well as the small sample size of our population. Conversely, patients splenectomized for idiopathic thrombocytopenia or patients taking immunosuppressive treatment were those completely vaccinated.

The prevention and infection rates in immunocompromised children and young adult patients was also specifically studied. A good adherence to guidelines in this group was observed, especially in children splenectomized for haemolytic anemia excepting hemoglobinopathy (paediatric haematology ward).

In the same way, comparing practices in adults and children populations, it was noticed that 65% of children and 75% of adults were vaccinated against *S. pneumoniae*, 89% of children and 37% of adults against *H. influenzae* B, 45% of children and 10% of adults against *Neissseria meningitidis*. 40% of children and 4% of adults only had all vaccinations, 23% of children and 35% of adults had none. Concerning antibioprophylaxis, 90% of children and 64% of adults received a prescription. 6% of children presented an OPSI, compared to 10% of adults.

Several observations may explain these findings. These children were followed by specialized physicians well aware of the risk of OPSI. Further, these children were receiving long-term antibioprophylaxis (mostly cotrimoxazole) which may also protect against some encapsulated bacteria such as *S. pneumoniae*.

Table 4 Anti infectious prophylaxis rate obtained in hospitals and prescribed by primary care practitioners.

	Hospital: 154 (percentage)	GP: 46 (percentage)
Pneumococcal immunization	109 (70.8)	38 (82.6)
Meningococcal immunization	37 (24)	*No data*
Haemophilus immunization	51 (44)	*No data*
Antibioprophylaxis	114 (74)	4 (66.7)
Antibiotic in case of fever	20 (13)	4 (8.7)
Information about infections	30 (19.5)	30 (65.2)

GP: general practitioner.

One of the specificities of this study was to include children from a large European centre for treatment of primary immunodeficiencies. Immunocompromised patients represent 65.6% of our population, which is higher than in other studies, this bias could explain the higher mortality rate (11.7%) compared to other studies. Applying rules of prevention for those susceptible patients remains important. However, few data are available about the efficacy of the vaccination in immunocompromised hosts, and the guidelines for OPSI prevention in this group of patients remain elusive. Yet, in immunocompromised patients, the application of guidelines and the use of vaccination and antibioprophylaxis is able to avoid some infection and especially infection with encapsulated bacteria. This work highlights the fact that departments that were involved in managing this kind of patients were more effective in applying recommendations.

The small size of this population did not permit for the study of the characteristics of OPSI: only 13 infectious events were recorded, in particular no pneumococcal infection (explained partially by the good rate of vaccine).

Taking these observations into consideration, how can patient care be improved? Written protocols should be used by all teams managing asplenic patients. A letter can be given to patients with information about immunization, antibiotic prophylaxis, and recommendations in case of fever. It also seems important for the medical unit in charge of splenectomized patients to contact the general practitioner for information about the infectious risks associated with asplenism. Prevention has to be stressed to the patient (life-long infectious risk) and pneumococcal vaccination done at least every 5 years with new vaccine trials to be generated to better induce immunological protection.

Some authors recommended spleen registry [9], to improve adherence to recommended guidelines. In Melbourne, the Victorian Spleen Registry registers splenectomized patients since 2003, and sends them recommendations and educational resources, and annual reminders about vaccinations. Data from this registry in 2007 showed a 59% adherence to antibiotics, which is better than published data.

Conclusion

In this study, 8.4% of the population presented an infectious event requiring hospitalization. On the other hand, GPs' knowledge about pneumococcal appeared to be good, and the role of the GP is critical GP in education and prevention of infectious risk in splenectomized patients, throughout their lives. Specific attention should be paid to immunocompromised patients, who require stringent immunizations and education, and special vigilance is required for patients splenectomized for trauma or solid tumor (adults) and for hemoglobinopathy (children).

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