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REVIEW

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Recommended vaccinations for asplenic and hyposplenic adult patients

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ABSTRACT

Asplenic or hyposplenic (AH) individuals are particularly vulnerable to invasive infections caused by encapsulated bacteria. Such infections have often a sudden onset and a fulminant course. Infectious diseases (IDs) incidence in AH subjects can be reduced by preventive measures such as vaccination. The aim of our work is to provide updated recommendations on prevention of infectious diseases in AH adult patients, and to supply a useful and practical tool to healthcare workers for the management of these subjects, in hospital setting and in outpatients consultation. A systematic literature review on evidence based measures for the prevention of IDs in adult AH patients was performed in 2015. Updated recommendations on available vaccines were consequently provided. Vaccinations against *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b and influenza virus are strongly recommended and should be administered at least 2 weeks before surgery in elective cases or at least 2 weeks after the surgical intervention in emergency cases. In subjects without evidence of immunity, 2 doses of live attenuated vaccines against measles-mumps-rubella and varicella should be administered 4–8 weeks apart from each other; a booster dose of tetanus, diphtheria and pertussis vaccine should be administered also to subjects fully vaccinated, and a 3-dose primary vaccination series is recommended in AH subjects with unknown or incomplete vaccination series (as in healthy people). Evidence based prevention data support the above recommendations to reduce the risk of infection in AH individuals.

KEYWORDS

asplenic; hyposplenic; infectious diseases; prevention; recommendations; splenectomy; vaccinations

Introduction



The spleen is crucial in regulating immune homeostasis through its ability to link innate and adaptive immunity and in protecting against infections. The term “asplenia” refers to the absence of the spleen, a condition that is rarely congenital and mostly post-surgical (due to splenic rupture from trauma or for haematological, immunological, or oncological reasons). The impairment of splenic function is defined as hyposplenism, an acquired disorder caused by several diseases (haematological and immunological disorders, malaria, splenic vein thrombosis, infiltrative diseases such as sarcoidosis, amyloidosis, tumors or cysts). Asplenia and hyposplenism are important risk factors for invasive infections in particular with encapsulated bacteria as *Streptococcus pneumoniae* (responsible for more than 50% of infections), *Haemophilus influenzae* type b, *Neisseria meningitidis*. The term “overwhelming post-splenectomy infection” (OPSI) refers to a rapid fatal syndrome occurring in individuals following removal of the spleen, but is largely interchangeable with “asplenic sepsis.” OPSI can progress from a mild flu-like illness to fulminant sepsis in a short time period and has high mortality rate (up to 50% despite maximal treatment).¹ Estimated incidence of OPSI is around 0.23–0.42% per year, with a lifetime

risk of 5%.² Although the risk of OPSI has been reported potentially life-long,^{3,4} is commonly accepted that the highest frequency of life-threatening infectious episodes is observed during the first 2 y (near 30% of episodes occur within the first year after splenectomy and 50% within the first 2 years).^{5–7}

The infectious risk is higher in subjects affected by haematological diseases as sickle cell anaemia and thalassemia major or lymphoproliferative disorders (e.g. Hodgkin’s disease, non-Hodgkin’s lymphomas etc.).^{8,9}

Furthermore, age at time of splenectomy seems to play an important role in determining risk of infection: incidence of OPSI is higher in patients younger than 16 y (particularly younger than 5 y).^{2,9} The mainstays of infectious diseases prevention in asplenic and hyposplenic (AH) subjects include: 1) patient and family education, 2) vaccinations, 3) prophylactic antimicrobial therapy in selected people, 4) early empirical antimicrobial therapy for febrile episodes, 5) early management of animal bites, 6) malaria prophylaxis for travelers in endemic countries.

The past decade has seen increased efforts to highlight the risks of infection in asplenic patients, to improve general awareness, and to give advice on appropriate precautions to prevent OPSI. Despite all such efforts, reports of OPSI cases continue to occur.¹

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The aim of our work is to provide updated recommendations on prevention of infectious diseases in AH adult patients, and to supply a useful and practical tool to healthcare workers for the management of these subjects. Therefore, in 2015, we performed a literature review in Medline using the keywords “asplenic” or “hyposplenic” combined with “prevention” or “vaccination.” Overall 95 papers were selected and reviewed. In particular, we focused on available vaccines, the schedule and timing for doses administration, and antibiotic prophylaxis. These recommendations are also based on the consensus and opinion of the authors, who are experts in the fields of immunology, infectious diseases and public health. Results of the literature review are reported in the following sections and a summary of recommendations, is shown in Table 1.

Pneumococcal vaccination

There are 2 types of pneumococcal vaccine currently available for adults in Italy: - Pneumococcal 13-valent conjugate vaccine (PCV13), contains polysaccharides from different capsular types of *S. pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F). These polysaccharides are conjugated to the CRM197 carrier protein and adsorbed on aluminum phosphate. PCV13 is

authorized for all ages; it is approved for the prevention of pneumococcal pneumonia, pneumococcal invasive disease and, in subjects under 18 years, also for otitis.

- Pneumococcal polysaccharide vaccine (PPSV23), contains purified capsular polysaccharide from 23 capsular types of *S. pneumoniae* (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F). This vaccine is authorized for people aged >2 y. PPSV23 is approved for the prevention of pneumococcal invasive diseases.

Conjugate vaccines elicit a T-cell dependent immune response and is more immunogenic than vaccines with polysaccharides alone;¹⁰ it induces long-term protection, immunologic memory and has boosting effect with a better immunologic response when used for priming.^{11,12} Furthermore, PCV13 seems to be immunogenic if used as a booster dose in patients with previous PPSV23 vaccination.¹³ A recent study suggests that conjugated vaccine may be the most suitable choice to generate IgG-mediated protection in asplenic patients.¹⁴ Polysaccharide vaccine elicits T cell independent immune responses, it is a poor inducer of immunologic memory and it is associated with immunological hyporesponsiveness to subsequent vaccinations. The immune response is poor or inconsistent in children aged < 2 y and in patients with immune deficiency.

Table 1. Indications, doses, timing of the main vaccinations and booster doses in asplenic subjects or candidates for splenectomy.

Vaccine	Indications and doses	Timing of vaccination	Booster doses
Pneumococcal	<ul style="list-style-type: none"> ✓ Naïve subjects: PCV13 (1 dose) followed by PPSV23 (1 dose) at least 8 weeks later. ✓ In patients who have previously received PPSV23, administer PCV13 ≥ 1 year later. ✓ In patients who have previously received PCV13, repeat 1 dose of PCV13 followed by PPSV23 ≥ 8 weeks later. 	<ul style="list-style-type: none"> In case of splenectomy: -At least two weeks before elective surgery^{4,5} -After two weeks post-operatively in emergency cases 	PPSV23: 1 dose 5 years after PPSV23
Meningococcal	<ul style="list-style-type: none"> ✓ Naïve subjects: 2 doses of Men ACWY conjugate vaccine given 8–12 weeks apart from each other.¹ ✓ In patients previously vaccinated with a single dose of Men ACWY or Men C, repeat the entire cycle (2 doses 8–12 weeks apart from each other)¹ ✓ Men B vaccine: 2 doses administered at least 2 months apart from each other. 	In case of functional asplenia: as soon as possible	Men ACWY: 1 dose every 5 years MenB: not recommended
<i>Haemophilus influenzae</i> type b	<ul style="list-style-type: none"> ✓ Naïve subjects: 1 dose of conjugate Hib vaccine¹ ✓ In subject previously vaccinated, repeat 1 dose of conjugate Hib vaccine¹ 		Not recommended
Influenza	<ul style="list-style-type: none"> ✓ Administer 1 dose of flu vaccine 		Yearly (October)
Measles Mumps Rubella	2 doses of MMR administered 4–8 weeks (preferably three months) apart from each other in subjects without evidence of immunity ^{2,3}		Not recommended
Varicella	2 doses of V-containing vaccine administered 4–8 weeks (preferably three months) apart from each other in subjects without evidence of immunity ^{2,3}		Not recommended
Tetanus diphteria pertussis	<ul style="list-style-type: none"> ✓ Naïve subjects or subjects who are not fully vaccinated (3 doses): repeat the entire cycle ✓ In subjects previously vaccinated with a primary cycle: 1 booster dose 		1 Dose every 10 years

¹Administration of vaccines outside the age groups indicated in the Summary of Product Characteristics (SPC) must be motivated, shared with the patient and recorded.

²The subjects are defined as “previously vaccinated” on the basis of medical history data (previous infection) or vaccination certificate. In dubious cases it is necessary to carry out a determination of serum antibody titer.

³In patients with concomitant immunosuppressive diseases or treatment with immunosuppressive drugs it is necessary to evaluate case by case, the decision to administer live viral attenuated vaccines. Under such conditions, specialists in the field should be consulted.

In general:

-Subjects with lymphocyte deficit should not receive live viral attenuated vaccines.

-Subjects with neutropenia should not receive live attenuated bacterial vaccines.

⁴Preferably 4–6 weeks prior to splenectomy.

⁵In case of chemo- or radio therapeutic treatment vaccinations should be administered at least 2 weeks before or 3 months after the treatment.

A recent study shows that PPSV23 may deplete the preexisting pool of peripheral memory B cell because polysaccharide antigens drive memory B cells into terminal differentiation without reintegrating the memory B-cell pool.¹⁵ Failures of PPSV23 vaccine have been reported. In asplenic patients it can be due to underlying condition (i.e. hematological malignancies) or to immunosuppression. Some authors hypothesize that a poor antibody response may be genetically regulated.¹⁶⁻¹⁸

We recommend the following pneumococcal vaccine strategy for asplenic adults. In naïve patients administer PCV13 (1 dose) followed by PPSV23 at least after 8 weeks to extend serotype coverage. Some experts suggest to repeat 1 dose of PCV13 1 y after PPSV23, to restore the memory B cell pool.^{14,15,19} In patients who have previously received PPSV23, administer PCV13 at least 1 y after the PPSV23.^{20,21} Asplenic patients who previously received one or more doses of PPSV23 had a dose (negative) and time (positive) related response.¹⁹ Conjugate vaccine seems to be able to restore the memory B-cell pool decreased by a previous PPSV23 dose,¹⁵ but the timing and dosing required have not been clearly determined yet.^{19,20} In patients who have previously received PCV13, administer PPSV23 at least 8 weeks after PCV13. Repeat one dose of PCV13 if the previous dose was given more than 5 y before, then administer PPSV23 at least after 8 weeks. PCV13 should be administered first. Administer a second dose of PPSV23 at least 5 y after the first dose of PPSV23.^{22-24,25}

Ideally patients should receive pneumococcal vaccine from 4 to 6 weeks before elective splenectomy or initiation of chemotherapy or radiotherapy.

If it is not possible, vaccination should be administered at least 2 weeks pre-operatively in elective cases or at least 2 weeks post-operatively in emergency cases.^{17,22,24}

In case of chemotherapy or radiotherapy administer vaccines at least 2 weeks before treatment or 3 months after. Doses administered during chemotherapy cannot be considered effective.^{23,26,27}

Vaccination is administered by intramuscular injection. Under specific conditions, it can be given also as a subcutaneous injection. The preferred injection site in adults is the deltoid muscle.

PPSV23 safety was assessed both for immediate adverse reaction and for long-term ones. PCV13 seems to have a similar profile risk, even if data on long-term adverse reaction in adults are not available. Common reactions reported include fever, irritability, injection site erythema, induration/swelling or pain/tenderness, decreased appetite, sleep disturbances. Infrequent reactions include rash, anaphylactic reaction, shock and angioedema. Lymphadenopathy at the injection site is very rare.²³

Contraindications for both PCV13 and PPSV23 vaccine are a confirmed anaphylactic reaction to a previous dose of the vaccine or a confirmed anaphylactic reaction to any component of the vaccine.

Precautions to be taken are pregnancy, acute severe or moderate illness with or without fever, allergic reaction to the latex (if in the syringe) and only for PPSV23 previous doses of the same vaccine.^{28,29}

Meningococcal vaccination

Meningococcal vaccines commercially available are conjugated vaccines (linked to a protein to make them more effective and

immunogenic) and inactivated (obtained from the bacterium fragments). Vaccination is administered by intramuscular injection. Conjugate formulation provides immunological memory and protection of longer duration than polysaccharide vaccines.³⁰

In Italy the following types of meningococcal conjugate vaccines are available:

- 1) monovalent conjugate vaccines against serotype C (MenC). They are used in children as young as 2 months of age, adolescents and adults. They are available in formulations: a conjugate vaccine with the carrier protein CRM197 of *Corynebacterium diphtheriae* and an oligosaccharide conjugate vaccine with the carrier protein CRM197 *Corynebacterium diphtheriae*;
- 2) tetravalent conjugate vaccine (Men ACWY), which protects against meningococcal serotypes A, C, W135 and Y; it is available in 2 formulations: conjugated to *Corynebacterium diphtheriae* CRM197 protein that is used in children (aged 2 y old), adolescents and adults and conjugated to the tetanus toxoid carrier protein that is used in subjects from 12 months of age and older;
- 3) vaccine against meningococcal serogroup B, developed with the “reverse vaccinology” technique, are based on the study of the bacterial DNA. The vaccine is formed by 4 antigenic components of *N. meningitidis* group B exposed on the surface of the bacterium: the recombinant fusion protein NHBA (Neisseria Heparin Binding Antigen), the recombinant protein NadA (Neisseria adhesin A), the recombinant fusion protein fHbp (factor H binding protein), the outer membrane vesicles (OMV) of the bacterial strain NZ98 / 254 measured as the amount of total protein containing Pora P1.4. It is used in individuals from 2 months of age and older.^{31,32}

The immunogenicity of conjugated meningococcal vaccines is evaluated in terms of serum bactericidal activity (SBA) and measured by geometric mean titre (GMT).³³ Despite the lower levels of antibodies produced by AH patients following vaccination than those produced by healthy immunocompetent subjects, 80% of them reaches SBA values equal to or exceeding the threshold value of protection,^{33,34} particularly after the administration of a second dose of vaccine.³⁵⁻³⁷

A quadrivalent conjugate meningococcal vaccine is the preferred choice for protection against meningococcal diseases of subjects at risk, as AH adults patients.

Such patients should receive a primary series of Men ACWY of 2 doses given 8–12 weeks apart. Based on the technical details, the vaccine is indicated for subjects aged between 2 and 55 y old. Vaccination of older subjects must be motivated, shared with the patient and recorded.³³ Booster doses should be given every 5 y to asplenic patients in order to maintain a high level of protective circulating antibodies.^{30,33,38,39}

In adults, is recommended the administration of 2 doses of vaccination against meningococcus B at least 2 months apart; there are no evidence at this time to recommend booster doses.²⁴

All patients who must undergo elective splenectomy should receive a dose of meningococcal conjugate vaccine at least 2 weeks before surgery to optimize the immune response;^{26,39} if it is not possible to respect this timing, it is recommended to carry out the vaccination at least 2 weeks after surgery.⁴⁰⁻⁴³

For asplenic subjects requiring chemotherapy, vaccination should be performed at least 2 weeks before starting treatment or 3 months after the end of therapy; doses of vaccine administered during chemotherapy cannot be considered effective.²⁶

Meningococcal vaccines have been formulated for intramuscular administration in the deltoid region in adolescents and adults.³² Meningococcal vaccines have a good safety profile. Adverse reactions following vaccination are usually mild and are mainly represented by erythema (19.7%), edema and pain at the injection site (13.7%), fever (16.8%), headache (16.0%), irritability, nausea, vomiting, rash, itching, illness, lymphadenopathy, hypotonia, paresthesia, fainting. There are few reports of hypersensitivity reactions (including anaphylaxis, bronchospasm and angioedema) and seizures.³⁰ Local and systemic reactions are of the same magnitude after the administration of the first dose or boosters.³³

Contraindications to the administration of meningococcal vaccines (including meningococcal C, Men ACWY and meningococcal B) are represented by a severe allergic reaction (anaphylaxis) to a previous dose of meningococcal vaccines or to a component of the vaccine (including tetanus toxoid or diphtheria).

The presence of acute illness, severe or moderate, with or without fever and / or severe allergic reaction to latex (for products that contain latex in the syringe) should be considered as precautions for administration of anti-meningococcal vaccines.^{29,30,32,33}

Pregnancy and breastfeeding do not represent conditions to postpone meningococcal vaccination in patients with asplenia; in fact, clinical risks due to the asplenic condition are higher than any eventual side effects resulting from vaccination.

Haemophilus influenzae vaccination

Currently, only protection against *Haemophilus influenzae* type b (Hib) strains is available; vaccines against non type b or non typeable strains do not exist. Hib vaccine consist of purified component of the bacterial capsule (polyribosyl ribitol phosphate; PRP). Conjugation of the PRP polysaccharide with protein carriers, that contain T-lymphocyte epitopes, confers T-lymphocyte dependent characteristics to the vaccine; this conjugation enhances the immunologic response to the PRP antigen and results in immunologic memory. There are actually 3 types of conjugate vaccine, utilizing different carrier proteins for the conjugation process, all of which are highly effective and safe: inactivated tetanospasmin (also called tetanus toxoid), mutant diphtheria protein, and meningococcal group B outer membrane protein. Hib conjugate vaccines are highly immunogenic: more than 95% of subjects will develop protective antibody levels after a primary series. Furthermore, clinical efficacy has been estimated at 95% to 100%.^{44,45}

Hib vaccine is also immunogenic in patients with increased risk for invasive disease, such as those who have had a splenectomy: case series show a modest increase in antibody responses after vaccination, but always above the protective level (0.15 µg/mL).^{42,45,46}

It is well known that vaccine-induced anti-PRP antibody levels decline over time below the putative protective threshold, but it is not clear whether the apparent decline in protection in

these patients may be accompanied by an increase in susceptibility to Hib disease.^{45,46}

However, specific studies of efficacy have not been performed in populations with increased risk of invasive disease.⁴⁴ International guidelines recommend administration of a single dose of any licensed Hib conjugate vaccine to unimmunized adults who are asplenic or who are scheduled for an elective splenectomy;^{26,47} taking into account the decline in antibody levels over time, some experts suggest administering a dose regardless of prior vaccination history.^{43,45,48} Considering the low reactogenicity and the low cost of anti-Hib vaccine, and the lack of access to the assessment of post-vaccination antibodies, we suggest vaccination against Hib in asplenic and hyposplenic subjects, regardless of the history of vaccinations in order to increase antibody titers. Currently, there is no evidence to recommend booster doses of Hib-vaccine.

Regarding the timing, vaccine should be administered at least 2 weeks before splenectomy in elective cases (preferably 4–6 weeks before) or at least 2 weeks after surgery in emergency case.^{26,39,42,43,47}

Hib-vaccine should ordinarily be administered as soon as possible after recognition of non-surgical hyposplenism but specific scheduling may be required in the context of recovery from any immunosuppression. In adult patients, Hib vaccines could be administered intramuscularly at the level of the deltoid.⁴⁷ Adverse reactions to Hib-vaccines are uncommon, usually mild (swelling, redness and pain at the punctio), and generally resolve within 12–24 hours.^{44,49,50} Systemic reactions such as fever, convulsions, irritability and cyanosis are uncommon and occur at the same frequency of DTaP vaccination; serious systemic reactions are rare (incidence rate of anaphylaxis from 0.65 to 3 per million vaccine doses administered).^{44,49} Vaccination with a Hib-containing vaccine is contraindicated in infants aged <6 weeks and among persons known to have a confirmed anaphylactic reaction to a previous dose of a Hib-containing vaccine, or to any components of the vaccine.⁵⁰

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation; if an individual is acutely unwell, immunisation may be postponed until they have recovered.⁵⁰

Hib-containing vaccines may be given to pregnant women when protection is required without delay; there is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids.⁵⁰

Influenza vaccination

Influenza vaccines are annually prepared using virus strains in line with the WHO recommendations, based on surveillance data indicating which viruses are circulating and forecasts about which viruses are the most likely to circulate during the coming season. Flu vaccines for adults are available either as a trivalent (containing 2 subtypes of influenza A and one B virus) or quadrivalent (with an additional B virus) injection. The vaccines contain inactivated viruses and induce protection after injection (typically intramuscular, though subcutaneous and intradermal routes can also be protective) based on an immune

response to the viral antigens. The influenza vaccination effort protection from influenza syndrome and secondary bacterial infection (particularly due to *S.pneumoniae* and *S.aureus*).^{39,51}

In asplenic patients, influenza immunization is associated with a 54% reduced risk of death compare with unimmunized asplenic persons.⁵² Therefore international guidelines recommend annual influenza vaccine for hyposplenic or asplenic patients; the vaccine could be administered before or after splenectomy, preferably in October to afford seasonal protection.^{26,39,43,53,54}

Redness, swelling, hardness at the injection site are the most common local reactions following immunization (about 15% after intramuscular vaccine, and 61% after intradermal vaccine); these symptoms may occur between 6 and 24 hours after vaccination and have short duration (maximum 2 days).⁵⁵ Systemic symptoms include mild flu-like manifestations (approximately 42% of subjects) and have the same duration of local symptoms. Anaphylactic reactions are rare.^{53,56}

Vaccination with influenza vaccine is contraindicated in persons known to have a confirmed anaphylactic reaction to a previous dose of the vaccine, or to any components of the vaccine. In recent years, inactivated influenza vaccines that are egg-free or have a very low ovalbumin content have become available and studies show they may be used safely in individuals with egg allergy.

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation; if an individual is acutely unwell, immunisation may be postponed until they have recovered.⁵³

A definite causal relationship between Guillain-Barré syndrome (GBS) and influenza vaccines has not been established; nevertheless it is to be considered as precaution an history of Guillain-Barré syndrome within 6 weeks before.⁵³

Tetanus, diphtheria, pertussis vaccination

Formulations of combined bivalent vaccines against diphtheria and tetanus (bivalent) or trivalent vaccines, with the addition of pertussis antigens or quadrivalent vaccine combined to IPV against poliovirus, or monovalent vaccines against tetanus are currently available on the market. After the full vaccination course and the following booster doses, efficacy of monovalent and combined vaccines is almost 100% against tetanus. In adults with unknown vaccination history 3 doses of dTap vaccine confer seroprotective titres against diphtheria and tetanus comparable to titres obtained after vaccination with Td, moreover the administration of multiple doses of dTap vaccine does not cause an increase in reactogenicity, compared with administration of the Td vaccine.⁵⁷⁻⁶¹

Indeed, booster doses with dTap induce an effective response against pertussis, with an increase of antibodies titres already after the first dose of vaccine, even in subjects never immunized. Thus, the immunological response to booster doses with pertussis-containing vaccines is effective even after natural acquired immunity in subjects who experienced contacts with *Bordetella pertussis* during their lifetime.^{62,63}

In fact, protection induced by pertussis vaccination decreases 4–12 y after the completion of a primary course and 4–20 y after natural infection, consequently incidence rates of

pertussis increase in adolescents and adults in absence of boosters. The majority of pertussis cases could be avoided with the introduction of early booster doses in adolescence and decennial boosters in adulthood.⁶⁴⁻⁶⁶ Therefore, even in AH subjects, previously vaccinated with a primary cycle, one booster dose with dTap is recommended, while in naïve subjects or subjects who are not fully vaccinated, the entire cycle should be repeated. Moreover, for AH adult subjects decennial booster doses with dTap vaccines are recommended, as for the general population.^{68,69}

In case of splenectomy, dTap vaccination should be administered at least 2 weeks before elective surgery, preferably 4–6 weeks, or after 2 weeks post-operatively in emergency cases. In case of functional asplenia dTap vaccination is recommended as soon as possible. In asplenic subjects requiring chemotherapy and radiotherapy treatment, dTap vaccination should be administered at least 2 weeks before or 3 months after the treatment. Vaccine doses administered during the treatment cannot be considered effective.²⁶

The dTap vaccine is administered by intramuscular injection at the level of the deltoid. Available vaccines for tetanus, diphtheria and pertussis have a good safety profile; adverse effects are usually mild and consist mainly in general reactions such as fever, drowsiness and irritability and in local reactions such as swelling (2%), erythema or edema (25–30%), pain at the injection site (50–85%). Many studies show an increased incidence of local reactions with an increase in the number of doses received, mainly due to the tetanus component. Guillain-Barré syndrome and brachial neuritis associated with the tetanus vaccination, have been described, but are extremely rare (respectively 0.4 cases per million doses and from 0.5 to 1 case per 100,000).⁵⁸

Contraindications for dTap vaccine are a confirmed anaphylactic reaction to a previous dose of the same vaccine or to any vaccine component. Temporary contraindications are represented by acute illness, severe or moderate, with or without fever and it is to be considered as precaution an history of Guillain-Barré syndrome within 6 weeks after the administration of a previous dose of vaccine.

The presence of severe allergic reaction to latex (for products that contain latex in the syringe), a peripheral neuritis and Arthus reaction after administration of a previous dose should be considered as precautions for administration of dTap vaccines.^{29,58}

Measles, mumps, rubella, varicella vaccinations

Live attenuated vaccines for the prevention of measles, mumps, rubella and varicella are available in Italy as combined trivalent (MMR) or quadrivalent (MPRV) vaccines. Monovalent vaccines against varicella (V) are also available in Italy. In order to reach a full protection 2 doses of vaccines are necessary in all ages. The time interval between the first and the second dose should be at least of 4–8 weeks; according to the epidemiological context, in absence of an increased risk, a longer interval (3 months) is desirable, as suggested by Canadian recommendations.⁷⁰

Protection afforded by a single dose of live attenuated measles containing vaccine is lifelong in most people. However, a

small percentage (2–5%) of immunized subjects do not develop immunity against measles after the first dose. A second dose assures protection against measles in more than 99% of subjects. As far as mumps, the antibody levels after vaccination decreased more than in the case of natural disease. The efficacy of a single dose varies from 61% to 91%, for the mumps component. The adoption of a 2 doses schedule in Finland and Sweden determined a net reduction of the disease, while in USA a 99% reduction of mumps cases was recently registered. With regard to rubella, seroconversion in vaccinated subjects is almost 100%; levels and duration (about 20 years) of antibody titer are similar to natural disease.⁷¹⁻⁷⁴

In all countries where varicella vaccination has been adopted a great reduction of incidence and hospitalization rates was observed.⁷⁵ The vaccine has an efficacy of 80–90% in preventing infection, and 85–95% in preventing severe varicella cases.⁷⁶ However, breakthrough varicella cases were observed in high-vaccinated populations and it is not clear if those cases are due to a primary (inability to develop a protective immune response after one dose of vaccine) or a secondary vaccine failure (waning immunity after a confirmed initial immune response).⁷⁷

For AH adults without evidence of immunity, vaccinations against MMR and V are recommended in 2 doses, administered 4–8 weeks (preferably 3 months) apart from each other. Subjects are defined as “previously vaccinated” on the basis of medical history data (previous infection) or vaccination certificate. In dubious cases it is necessary to carry out a determination of serum antibody titer.^{22,25,26,78-81} Usually, live attenuated vaccines are contraindicated in severe immunocompromised patients, while inactivated vaccines are strongly recommended in subjects with primary or secondary immunodeficiency.⁸²

In AH patients with concomitant immunosuppressive diseases or treatment with immunosuppressive drugs, it is necessary to evaluate case by case the decision to administer live viral attenuated vaccines. In general, subjects with lymphocyte deficit should not receive live viral attenuated vaccines; while subjects with neutropenia should not receive live attenuated bacterial vaccines. Under such conditions, specialists in the field should be consulted.

Regarding the timing, MMR or V vaccines should be administered at least 2 weeks before splenectomy in elective cases (preferably 4–6 weeks before) or at least 2 weeks after surgery in emergency case.²⁶

Vaccinations against MMR and V are administered by subcutaneous route in the deltoid region. Common reactions reported for these vaccinations include fever episodes, occurring 5–12 d after vaccination, injection site erythema or pain. Some of the characteristic symptoms of the natural disease such rash or swelling of the salivary glands and lymph nodes can be developed. The vaccine viruses are not transmitted from person to person like the corresponding natural virus: accordingly, the recently vaccinated subjects, even if they manifest the symptoms described above, are not contagious to others.⁸³⁻⁸⁶ On the contrary, for varicella cases, when a vesicular erythema is developed after vaccination, the content liquid can infect, by contact, a person who has never acquired the disease or who has never been vaccinated.⁸⁷ Contraindications to MMR or V vaccines include severe immunodeficiency

(blood cancers and solid tumors, congenital immunodeficiencies as agammaglobulinemic, common variable immunodeficiency or severe combined immunodeficiency; HIV with severe immunosuppression) and confirmed anaphylactic reaction to a previous dose of the same vaccine or to any vaccine component.

Temporary contraindications are represented by pregnancy, a severe or moderate illness, with or without fever, recent (at least 11 months) immunoglobulin administration except for post-exposure measles prophylaxis and long-term immunosuppressive therapy or transplantation of solid organ or staminal cells. The presence of severe allergic reaction to latex (for products that contain latex in the syringe), acute to moderate illness, history of arthritis after a first dose of MMR or rubella, history of thrombocytopenia or thrombocytopenic purpura after a first dose of MMR, especially if within 6 weeks and tuberculosis, should be considered as precautions for administration of MMR or V vaccines. Besides, for V vaccination precaution should be taken in case of severe or recurrent infections and use of aspirin or salicylates during the past 6 weeks.^{29,88}

Prophylactic antimicrobial therapy

The introduction of vaccination in subjects with functional or anatomic asplenia, has produced a significant reduction of infections with encapsulated bacteria. However, no vaccine reaches efficacy of 100%;⁸⁹ this led to consider adding prophylactic antibiotic therapy, typically oral penicillin twice a day, to prevent streptococcal and meningococcal infections.

However, data are lacking to inform decision making in many cases, because studies of the effectiveness of prophylactic penicillin have been limited to children with sickle cell disease.^{90,91} Moreover these studies were completed before the universal use of pneumococcal conjugate vaccines⁹² and before an increased prevalence of colonization and infection with penicillin-resistant pneumococci.

Currently, based on these data and as a precaution, the international guidelines recommend antibiotic prophylaxis in children younger than 5 y of age with asplenia for any reason.^{48,93}

Conversely, there is no evidence available from randomized control trials about efficacy of antibiotic prophylaxis in adults and experts suggest very different approaches.^{39,43,48,94}

As already mentioned, epidemiological data show an increased risk of OPSI in subjects with haematological diseases,^{8,9} in particular during the first years after splenectomy. For these reasons we suggest prophylactic antibiotic therapy in asplenic or hyposplenic adults affected by malignant haematological diseases (especially subjects who received irradiation of the spleen or affected by GVH) for a period of 2 y.

Concerning the antibiotic therapy, it is necessary to mention the management of febrile episodes: given the rapid evolution of OPSI, patients should have a standby of broad-spectrum antibiotics to start early empirical treatment in the event of any sudden onset of unexplained fever, malaise, chills or other constitutional symptoms, especially when medical review is not readily accessible.

Lastly, there is an increased risk of OPSI in patients with asplenia or hyposplenia who are bitten by dogs and other animals; the common causative organism is *Capnocytophaga*

canimorsus. Such patients should be warned of this risk and have adequate antibiotic cover following such bites, for example, amoxicillin/clavulanic acid for 5 d.⁹⁵

Conclusions

All asplenic and hyposplenic patients and their families should be educated and given written information about the risk of OPSI and strategies to minimize that threat, besides, their general practitioners should be informed for the management of infectious episodes. Vaccinations against *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b and influenza virus are strongly recommended and should be administered at least 2 weeks before surgery in elective cases or at least 2 weeks after the surgical intervention in emergency cases. In subjects without evidence of immunity, 2 doses of live attenuated vaccines against measles-mumps-rubella and varicella should be administered 4–8 weeks apart from each other; a booster dose of dTap vaccine should be administered also to subjects fully vaccinated, and a 3-dose primary vaccination series is recommended in AH subjects with unknown or incomplete vaccination series (as in healthy people). Early empirical antimicrobial therapy for febrile episodes is indicated for these patients; they should have a reserve or standby antibiotic supply with instructions to take in the event of any sudden onset of unexplained fever, malaise, chills or other constitutional symptoms. Prophylactic antimicrobial therapy is indicated in selected people. Currently, the use of antibiotics for prevention of infections in asplenic-hyposplenic adult patients is not evidence-based. An higher risk of OPSI is documented in asplenic subjects with haematological malignancies, especially in the first 2 y after splenectomy. Therefore, we suggest therapy with oral penicillin in this category of patients for a period of 2 y. Malaria prophylaxis for travelers in endemic areas is recommended to avoid severe complications of the disease. Travelers should take the best precautions to prevent infection by means of anti-malaric prophylaxis, mosquito repellents and other barrier precautions. Advice from an infectious disease physician or expert travel advisor is recommended before departure. Evidence based prevention data to reduce the risk of infection in AH individuals are accumulating and specific hospital protocols should be available to all healthcare workers in order to minimize the risk of infections potentially fatal in those fragile patients.

Abbreviations

AH Asplenic or hyposplenic patients
ID Infectious disease

Disclosure of potential conflicts of interest

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