Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: Prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haemato-Oncology Task Force

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Summary

Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen were first published by the British Committee for Standards in Haematology (BCSH) in 1996 and formally reviewed in 2002. Although the guidelines originated from discussion within the BCSH, the intended readership is wide given the multidisciplinary nature of the management of hyposplenism.

Keywords: splenectomy, infection, general haematology.

Key aspects of successive BCSH guidelines relate to identification of patients at risk of infection, patient information and education, immunization schedules, anti-infection prophylaxis, and treatment of proven or suspected infection. This guideline does not address the non-infective complications of splenectomy or functional hyposplenism.

This review replaces previous guidelines and updates and significantly revises the recommendations where necessary.

Patient groups considered at-risk include patients who have undergone surgical removal of the spleen and those with medical conditions that may predispose to functional hyposplenism.

A variety of methods are available as screening tools for functional hyposplenism. This area has recently been comprehensively reviewed and there is currently no easily applied technique available in routine practice that reliably identifies individuals at risk. This represents an area of unmet need.

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Vaccination should include the use of pneumococcal, *Haemophilus influenzae* type b (Hib), meningococcal and influenza vaccines.

Lifelong antibiotic prophylaxis is appropriate for high-risk groups. Low-risk patients should be counselled as to the risks and benefits of prophylaxis particularly where adherence is an issue.

Recommendations for the treatment of suspected or proven infection should be based on local protocols and should take into account relevant antimicrobial resistance patterns.

There is an identified need for further research into the effectiveness of vaccination in the hyposplenic patient and audit of infective episodes in this patient group should continue long term. No single group is ideally placed to conduct an audit into complications arising from hyposplenism but consideration should be given to the establishment of appropriate multidisciplinary networks. In UK practice this may best be embedded in Public Health Medicine but it is acknowledged that alternative arrangements may have equal validity.

Key recommendations

- Patients should be given appropriate written or electronic information and carry a card to alert health professionals to the risk of overwhelming infection. Patients may wish to invest in an alert bracelet or pendant (C).
- Patients should be educated as to the potential risks of overseas travel, particularly with regard to malaria and unusual infections, for example those resulting from animal bites (B, C).
- Patients records should be clearly labelled to indicate the underlying risk of infection. Vaccination and re-vaccination status should be clearly and adequately documented (C).

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- Local Health Care providers should maintain and up-date a register of at-risk patients. In UK practice it is suggested that this is most appropriately done through the patient's primary care record and provider (C).
- All splenectomized patients and those with functional hyposplenism should receive pneumococcal vaccination, *Haemophilus influenzae* type b conjugate vaccine and meningococcal conjugate vaccine (B, C). Influenza immunization should be undertaken yearly (C).
- Response to pneumococcal vaccination and the timing of pneumococcal revaccination may, where validated assays are available, be determined by levels of protective antibody (B, C).
- Lifelong prophylactic antibiotics should be offered to patients considered at continued high risk of pneumococcal infection using oral penicillins or macrolides (B, C). This advice should be regularly reviewed in the light of local pneumococcal resistance patterns (B, C).
- Patients not at high risk should be counselled regarding the risks and benefits of lifelong antibiotics and may choose to discontinue them (C).
- All patients should carry a supply of appropriate antibiotics for emergency use (C).
- Patients developing infection, despite the above measures, must be given systemic antibiotics and admitted urgently to hospital (B, C).

Grades of recommendation

A. Requires at least one randomized controlled trial, as part of the body of literature of overall good quality and consistency addressing the specific recommendations.
B. Requires the availability of well-conducted clinical studies, but no randomized clinical trials on topic of recommendation.
C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

These grades of recommendations have now been widely adopted, but originate from the US Agency for Health Care Policy and Research.

Background

Individuals with an absent or dysfunctional spleen are at increased risk of severe infection. The commonest pathogen is *Streptococcus pneumoniae*, but other organisms also present significant risks, including *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis*.

Overwhelming infection in hyposplenic or asplenic patients thus remains an area of concern. The original BCSH guideline on the prevention and treatment of infection in patients with an absent or dysfunctional spleen was published in 1996 (BCSH, 1996) and up-dated in 2002 (Davies *et al*, 2002).

Given the long time-interval and consequent changes in practice the reconvened guideline group has, on this occasion, completely revised the original guideline.

Methods

The members of the writing group were selected to be representative of UK-based medical practice. The writing group wish to acknowledge the additional input into the guidelines provided by discussion within the Health Protection Agency and the Royal College of General Practitioners. Medline (2001–2010) and the current Cochrane Library were searched for publications in English using the original keywords: infection, splenectomy, asplenia, vaccination, and hyposplenism. Relevant identified abstracts were reviewed and cross-checked. In addition, studies identified as part of the original guideline (BCSH, 1996) and update (Davies *et al*, 2002) were re-examined for relevance.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemato-Oncology Task Force of the BCSH. The guideline was then reviewed by a sounding board of approximately 100 UK haematologists, the BCSH and the British Society for Haematology Committee and the comments incorporated where appropriate.

Criteria used to quote levels and grades of evidence where specified are as outlined in appendix 3 of the Procedure for Guidelines Commissioned by the BCSH (www.bcshguidelines.com). Clinical trials have provided very little evidence to inform these guidelines.

Most of the recommendations that follow are based on the outcomes of large observational studies and evidence from expert committee reports and/or the clinical experiences of respected authorities and are therefore grade C, level IV.

Risk groups and screening

Hyposplenism may result from surgical removal of the spleen (for any reason), from therapeutic splenic embolization and as a complication of certain medical conditions or their treatment. This area has recently been comprehensively reviewed (William & Corazza, 2007; William *et al*, 2007). The risk of infection after splenectomy is well documented and a spectrum of infecting micro-organisms may cause serious infections.

There may be an additional risk to splenectomized individuals in terms of occupational exposure to certain pathogens, for example, those who work closely with domestic animals. There are no firm data on which to base recommendations but it would seem reasonable to ensure, as far as is practical, that both employers and employees are aware of the implications of exposure to potentially infective biological material. (Deshmukh *et al*, 2004).

The diagnosis and management of hyposplenism arising in the non-surgical context is less well documented but there is a practical need to identify patients at risk (Thomas *et al*, 2008; Ludvigsson *et al*, 2008). Certain medical conditions, such as sickle cell disease, are accompanied by functional hyposplenism and on this basis alone warrant appropriate management (Riddington & Owusu-Ofori, 2002). Other similar categories of patients include those with active chronic graft-versus-host disease (GvHD) and patients who have received therapeutic splenic irradiation (Kulkharni *et al*, 2000; Engelhard *et al*, 2002). For other patients, including those with medical conditions predisposing to hyposplenism (William & Corazza, 2007), various techniques have been used to determine the presence or absence of functional hyposplenism, including functional imaging, with scintigraphy of $_{99m}$Technetium-labelled heat-damaged autologous red cells detected on modern gamma cameras being considered the gold standard (De Porto *et al*, 2010),. In practical terms however only two techniques are readily routinely applicable outside the research environment.

- Examination of the peripheral blood for red cell changes associated with hyposplenism using phase contrast microscopy appears sensitive and specific (Cuthbert *et al*, 1995). Although the technique is straightforward it is not standard. Comparative studies suggest that enumeration of Howell-Jolly bodies in red cells using routine staining which is universally available and which correlates well with phase microscopy but not with functional imaging (Corazza *et al*, 1990), may not be sufficiently sensitive to detect those patients at risk of major infection (De Porto *et al*, 2010). Alternative methods of Howell-Jolly body enumeration using flow cytometry or argyrophilic staining may be more sensitive but are not yet routinely available (De Porto *et al*, 2010).
- A significant reduction in spleen size on anatomical imaging either by ultrasound or computed tomography scanning may also predict for functional hyposplenism and risk of infection, at least in the context of haemopoietic stem cell transplantation (Picardi *et al*,1999). This preliminary observation has not however been formally correlated with peripheral blood findings and functional imaging in other medical disorders. Accordingly, it remains unclear whether non-functional anatomical imaging alone adds any useful information in the context of suspected hyposplenism.

Recommendations

- **Patients who have undergone splenectomy or have medical conditions (see above) known to confer a major risk of hyposplenism do not require additional screening and should be managed accordingly (B, C).**
- **There is no routine, easily applicable method currently recommended for screening patients with other medical conditions known to predispose to hyposplenism and red cell scintigraphy remains the gold standard for evaluating potential functional hyposplenism in these patients. The development of a robust, standardized and easily applied test for functional hyposplenism would be of obvious advantage as a screening tool and this remains an unmet need. (C).**

Education and information

It remains essential to educate patients regarding the risk and the importance of prompt recognition and treatment of infections. Where available, information should be offered in both written and electronic form.

Patients should be encouraged to wear an alert bracelet or equivalent and carry a card with information about their condition, other clinical details, and contact telephone numbers. In an emergency this information may be life-saving.

Patients should be educated about the risks of animal bites and potential risks of tick and mosquito-borne diseases.

Travel to areas where malaria is endemic carries some risk and patients should be made aware of this. People at such risk need precise information about correct chemoprophylaxis relevant to local patterns of resistance and advice about measures to reduce exposure to mosquito bites (Oniyangi & Omari, 2006).

Education of both medical personnel and patients about the risks of sepsis in patients with an absent or dysfunctional spleen should be addressed. Patients are not always followed up in hospital and their primary care physician may take responsibility. Adults who had a splenectomy many years ago may not be aware of the risks and may never have been offered antibiotic prophylaxis or vaccination. The establishment of appropriate patient registries may offer both clinical and cost benefits in this regard (Spickett *et al*, 1999; Woolley *et al*, 2006).

Patients and their relatives should be aware that, despite pneumococcal vaccine and prophylactic antibiotics, breakthrough pneumococcal infection may occur and when unwell patients should seek and follow appropriate medical advice.

Anti-infection prophylaxis

The prevention of infection in patients without a functioning spleen has, and still does, depend(ed) on three major strategies. Firstly education of the patient as discussed above. Secondly the adoption of appropriate vaccination schedules and thirdly the use of prophylactic antibiotics providing pneumococcal cover.

Pneumococcal vaccination

Normal inoculations, including live vaccines, can be given safely to children or adults with an absent or dysfunctional spleen and vaccination against a range of potential pathogens has become accepted practice (Department of Health, 2010).

Hyposplenic individuals, especially young children, have a high risk of invasive infections caused by encapsulated

organisms (particularly *Streptococcus pneumoniae*, Hib and *Neisseria meningitidis*) and, at the same time, have an inherently reduced ability to mount protective antibody responses to polysaccharide antigens, which may result in vaccine failure. There are over 90 different serotypes of *S. pneumoniae*, of which at least 30 can cause invasive disease in humans. The mainstay of pneumococcal vaccination has, for many years, been the polyvalent polysaccharide pneumococcal vaccine (PPV), which provides short-term immunity against 23 pneumococcal serotypes (Vila-Corcoles *et al*, 2009). Despite appropriate efforts, some patients remain unvaccinated, while true vaccine failures also contribute to pneumococcal infection (Shetty *et al*, 1998; Meerveld-Eggink *et al*, 2008).

Failure to mount an antibody response may be genetically determined but is also more common in older patients and those splenectomized for haematological malignancies (Cherif *et al*, 2006; De roux *et al*, 2008). A failure to demonstrate a rise in titre of anti-pneumococcal antibody identifies non-responders who are at high risk of invasive pneumococcal disease (Musher *et al*, 2005).

Repeat vaccination is safe in responders and the need for revaccination may be based on measurement of antibody levels (Landgren *et al*, 2004; Stanford *et al*, 2009). True non-responders may derive no benefit even from further vaccination attempts with a conjugate vaccine (Musher *et al*, 2005).

Unlike polysaccharide vaccines, covalent linkage of polysaccharide to a carrier protein (conjugation) can significantly enhance immunoprotection against the polysaccharide by inducing a T cell-dependent immune response. Conjugate vaccines are highly immunogenic in infants as young as 2 months of age, provide higher antibody titres and induce immunological memory. A 7-valent pneumococcal conjugate vaccine (PCV7) that helps protect against the seven most prevalent pneumococcal serotypes (Adamkiewicz *et al*, 2008) was introduced into the UK national childhood immunization programme in September 2006 and, in April 2009, was replaced by a 13-valent pneumococcal conjugate vaccine (PCV13) (Stanford *et al*, 2009). As predicted, PCV13 is more immunogenic than PPV albeit with a more limited repertoire, and is highly effective in preventing invasive disease caused by the 13 serotypes included in the vaccine. There are, however, concerns that other pneumococcal serotypes may eventually replace those that are being eradicated by PCV13 (Singleton *et al*, 2007; Hicks *et al*, 2007) and argues strongly for the development of further extended valency conjugate vaccines. Conjugate vaccines are immunogenic in hyposplenic individuals and have been administered safely both before and after polysaccharide vaccines post-splenectomy (Smets *et al*, 2007), but the optimum scheduling is unknown.

In children with sickle cell disease a sequential regime based on three doses of PCV7 followed by PPV was highly effective in terms of antibody response (Reinert *et al*, 2007). However, in otherwise healthy children, a booster dose of PPV added limited serological benefit to two doses of PCV7 (Balmer *et al*, 2007a). However, PCV may have a role in PPV failures (Rose *et al*, 2005), although repeated prior administration of PPV may reduce the response to subsequent PCV administration (Orthopoulos *et al*, 2009).

A recent study has addressed immune responses to PCV7 in asplenic individuals greater than 5 years of age. A high degree of previous serological response to PPV was evident at baseline in this group. PCV7 administration produced a further increase in antibody directed against those serotypes within the PCV7 vaccine. Further PPV administration at 6 months post PCV7 was not associated with any additional benefit (Stanford *et al*, 2009).

The distillation of these data leads to a number of evidence-based conclusions although not all data pertain specifically to hyposplenic patients and management advice must accordingly be based on extrapolation. Increasingly in the UK, conditions leading to medical hyposplenism, particularly the sickle syndromes, will be detected in early childhood via screening programmes while other children who undergo splenectomy, or who develop functional hyposplenism will already have received the pneumococcal conjugate vaccine.

It should be recognized that this is a rapidly evolving field and recommendations around current UK practice are updated regularly. Current advice should always be the first point of reference (Department of Health, 2010). (Please see Table I.)

- In young children, sequential PCV vaccination appears effective and there appears to be no harm in PPV boosting, at age 2 years, in individuals at high risk of invasive pneumococcal disease (Lin *et al*, 2005).
- Hyposplenic children aged 2–5 years should receive one dose of PPV if previously fully immunized with PCV13 (3 doses at 2, 4 and 13 months), 1 dose of PCV13 followed by PPV 2 months later if previously immunized with PCV7, or 2 doses of PCV13 two months apart, followed by PPV 2 months later if previously unimmunized or partially immunized with any PCV. The additional benefit of PPV in this situation is, however, uncertain. The upper age limit for this approach is unknown but data on alternative approaches in children < 5 years of age is lacking.
- For older children and adults who may or may not have received previous PCV there is insufficient evidence to recommend a change in policy from PPV to PCV either for primary immunization or for boosting.
- There appears to be an increasing role for the measurement of serological response of antibody levels to common pneumococcal serotypes, particularly those included in PCV13. The World Health Organization (WHO) has recommended a serotype-specific IgG level of ≥0·35 μg/mL as a putative protective threshold following conjugate immunization in young children. The relevance of this threshold for adults, especially older people, is unclear and higher thresholds (e.g. ≥1·0 μg/mL) may be more appro-

Table I. Suggested schedule for immunization with conjugate vaccines in individuals with asplenia or splenic hypofunction.

Age at which asplenia or splenic dysfunction acquired	Vaccination schedule Where possible, vaccination course should ideally be started at least 2 weeks before surgery or commencement of immunosuppressive treatment.		
	Month 0	Month 1	Later
First presenting under 2 years	Complete according to national routine childhood schedule including booster doses of Hib/MenC and PCV13.	A dose of MenACWY conjugate vaccine should be given at least 1 month after the Hib/MenC and PCV13 booster doses.	After the second birthday, one additional dose of Hib/MenC and a dose of PPV should be given.
First presenting over 2 years and under 5 years (previously completed routine childhood vaccinations with PCV7)	Hib/MenC Booster PCV13	MenACWY conjugate vaccine	PPV (at least 2 months after PVC 13)
First presenting over 2 years and under 5 years (previously completed routine childhood vaccinations with PCV13)	Hib/MenC Booster PPV	MenACWY conjugate vaccine	
First presenting over two and under 5 years (unvaccinated or previously partially vaccinated with PCV7)	Hib/MenC vaccine First dose of PCV13	MenACWY conjugate vaccine	Second dose of PCV13 and then PPV (at least two months after PCV13)
First presenting over 5 years (regardless of vaccination history)	Hib/MenC vaccine PPV	MenACWY conjugate vaccine	

PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

priate (Stanford et al, 2009). Where individual laboratories have in place validated methods to determine serotype specific anti-pneumococcal antibody levels this may be used to guide decision-making (Balmer *et al*, 2007b).

- Patients who respond well serologically to PPV measured 4–6 weeks post-dose may be followed with serial antibody levels and boosted with PPV as required. It is known that antibody levels may decline rapidly over time, particularly in patients with sickle cell disease and lymphoproliferative disorders. Where available, measurement of serotype-specific pneumococcal antibodies can be used to monitor this decline and may be used to guide the timing of PPV revaccination.
- Alternatively, or where serotype-specific pneumococcal antibody testing is not available, PPV may be repeated at intervals of 5 years; however, this strategy does not detect non-responders who are at particularly high risk of invasive pneumococcal disease.
- The additional benefit of PCV vaccination in good serological responders to PPV is unclear and PCV vaccination should not therefore be routine in this group.
- Patients with sub-optimal or no serological response to PPV represent a high-risk group for invasive pneumococcal disease. They may benefit from PCV immunization immunization and, although two doses are commonly given, there is no standard recommended interval between them. A recent study in hyposplenic patients used a 4-week interval with good serological response (Rose *et al*, 2005).
- PPV should be given at least 2 weeks before splenectomy. Post-vaccination total antibody levels to pneumococcal antigens following splenectomy do not differ significantly from vaccinated normal control subjects, whether vaccination is undertaken immediately or at 14 d after splenectomy. Functional antibody responses are, however, better with delayed (14 d post) vaccination (Shatz *et al*, 1998). There are no data on the timing of PCV vaccination in young children who require elective or undergo emergency splenectomy, but it would seem appropriate to use similar timings for the first dose of PCV in this rare situation. Extreme care should be taken to ensure patients are not lost to follow up where first vaccination follows discharge from hospital.
- All other umimmunized patients at risk should be immunized at the first opportunity. In general, immunization should be undertaken no later than 2 weeks before immunosuppressive therapy and delayed at least 3 months after immunosuppressive chemotherapy or

radiotherapy or until recovery of adequate immunological function where this can be appropriately assessed (Pao *et al*, 2008).

Table I summarizes current guidance for vaccination of hyposplenic individuals against the three most important encapsulated pathogens based upon the age at which hyposplenism occurs.

Haemophilus influenzae type b vaccination

Haemophilus influenzae can be characterized as one of six different serotypes (a–f) or as non-typeable (also known as non-encapsulated) strains. *H. influenzae* serotype b (Hib) is the most virulent and, prior to routine immunization, accounted for over 80% of all invasive *H. influenzae* infections, mainly in children <5 years. The Hib conjugate vaccine was introduced into the UK childhood immunization programme in 1992 and resulted in a rapid and sustained reduction in the incidence of invasive Hib disease across all age groups through a combination of direct (vaccinated individuals) and indirect (herd immunity) protection; in 2009, there were only 59 cases reported in England and Wales. Hyposplenic individuals are at increased risk of invasive Hib disease although the risk is not as high as pneumococcal disease.

The current UK immunization schedule offers three doses of a Hib-containing combination vaccine (Pediacel®, Sanofi Pasteur MSD Ltd, Maidenhead, Berkshire, UK) at 2, 3 and 4 months of age, followed by a booster dose at 12 months, which is given as a Hib/Meningococcal group C (MenC) combination vaccine (Menitorix®, GlaxoSmithKline UK, Uxbridge, Middlesex, UK). In the UK, currently the Hib conjugate vaccine is only available in combination with MenC.

Recommendations for Hib vaccination for hyposplenic individuals are summarized in Table I.

Hyposplenic children aged <2 years should complete their vaccination according to the national immunization schedule and an additional booster of Hib/MenC should be given at the second birthday.

Hyposplenic children aged ≥2 years and adults should receive one dose of a Hib-containing vaccine (such as the Hib/MenC vaccine, Menitorix®), irrespective of their previous immunization status.

The timing of the first dose of vaccine is as for pneumococcal vaccination. It is recognized that hyposplenic individuals may show a blunted response to Hib conjugate vaccination compared with healthy controls, although whether this results in an increased risk of invasive disease is unclear (Pao *et al*, 2008).

Meningococcal vaccination

Meningococcal disease continues to cause significant morbidity and mortality across all age groups. Those with an absent or hypofunctional spleen are at particularly high risk of meningococcal disease. A meningococcal group C conjugate vaccine (MenC) was introduced into the UK childhood and adolescent immunization programme in 1999 and has resulted in a sustained reduction in invasive MenC disease across all age groups. In the UK, almost 90% of invasive meningococcal disease is caused by serogroup B. Other serogroups (particularly A, W135 and Y, for which a quadrivalent conjugate vaccine is licensed) account for only a small proportion of cases. Meningococcal group A disease is rare in Europe but causes large epidemics in other areas of the world.

The current UK immunization schedule offers two doses of MenC vaccine at 3 and 4 months of age, followed by a booster dose at 12 months, which is given as a Hib/MenC combination vaccine (Menitorix®) (Department of Health, 2010). In the UK, currently the MenC conjugate vaccine is available as a single vaccine (Menjugate®, Sanofi Pasteur MSD Limited, Maidenhead, Berkshire, UK, and NeisVac-C®, Baxter, Newbury, Berkshire, UK) as well as in combination with Hib (Menitorix®).

Recommendations for meningococcal vaccination for hyposplenic individuals are summarized in Table I. Recently, at least one quadrivalent MenACWY conjugate vaccine has been licensed for teenagers and adults in Europe. Based on experience with the MenC and other conjugate vaccines, the immunity provided by the quadrivalent MenACWY conjugate vaccine is expected to be higher and longer-lasting and to confer less risk of immunological tolerance than the plain polysaccharide quadrivalent meningococcal vaccine. For this reason, the quadrivalent MenACWY conjugate vaccine is recommended in preference to the plain polysaccharide meningococcal vaccine for all age groups (Snape *et al*, 2008). In time the quadrivalent MenACWY vaccine may be further anticipated to replace single MenC vaccination.

Off-label use of the quadrivalent MenACWY conjugate vaccine may be considered following appropriate Infectious Disease consultation in unimmunized or partially immunized hyposplenic/asplenic children aged <2 years considered particularly at risk of infection with non-C serotypes. In this situation, the quadrivalent MenACWY conjugate vaccine replaces component MenC conjugate vaccine at 3 and 4 months of age and is followed by the MenC conjugate vaccine (as the Hib/MenC combination vaccine, Menitorix®) at 12 months as well as the quadrivalent MenACWY conjugate vaccine booster one month later. An additional booster of Hib/MenC should be given at the second birthday.

Hyposplenic children aged ≥2 years and adults should receive one dose of a MenC conjugate vaccine (such as the Hib/MenC vaccine, Menitorix®) followed by a single dose of the quadrivalent MenACWY conjugate vaccine one month later, irrespective of their previous immunization status.

As discussed above, all hyposplenic individuals intending to travel to a country where there is an increased risk of serogroup A, W135 or Y disease should receive the quadrivalent MenACWY conjugate vaccine before travelling.

Influenza Vaccination

Given the risk of secondary bacterial infection, annual influenza vaccine continues to be recommended for hyposplenic or asplenic patients (Department of Health, 2010).

Recommendations

- **All patients should receive pneumococcal, *Haemophilus influenzae*** type b and meningococcal vaccination (A).
- **Vaccines should ideally be administered 2 weeks before or 2 weeks after splenectomy (B).**

- **Vaccines should ordinarily be administered as soon as practicable after recognition of non-surgical hyposplenism but specific scheduling may be required in the context of recovery from immunosuppression (B, C).**

Pneumococcal Vaccination

- This is a rapidly evolving field and reference should always be made to the latest Green Book (Department of Health, 2010) or equivalent advice.
- Infants aged <2 years should be immunized with three doses at the national schedule (2, 4 and 12 months), but should also be offered one dose of PPV at 2 years (B, C).
- Two to five year-olds: one dose of PPV if previously fully immunized with PCV13, 1 dose of PCV13 followed by PPV 2 months later if previously immunized with PCV7, and 2 doses of PCV13 two months apart, followed by PPV 2 months later if previously unimmunized or partially immunized with any PCV. The additional benefit of PPV in this situation is, however, uncertain. The upper age limit for this approach is unknown but data on alternative approaches in children <5 years of age is lacking (B).
- Children aged >5 years and adults: irrespective of immunization status should continue to receive one dose of PPV (C), with antibody response measured at 4–6 weeks if available (C).
- Responders should be revaccinated with PPV at 5-yearly intervals. Alternatively, where available, serotype-specific pneumococcal antibodies may be used to guide the timing of PPV revaccination.

- Serological non-responders to PPV may benefit from two doses of PCV 2 months apart (B, C).

Haemophilus influenzae b vaccination

- This is a rapidly evolving field and reference should always be made to the latest Green Book (Department of Health, 2010) or equivalent advice.
- Children aged <2 years should complete their vaccination according to the national schedule (B, C).
- Children aged ≥2 years and adults should be offered one dose of a Hib-containing vaccine (such as the Hib/MenC vaccine, Menitorix®), irrespective of their previous immunization status (B, C).

Meningococcal vaccination

- This is a rapidly evolving field and reference should always be made to the latest Green Book (Department of Health, 2010) or equivalent advice.
- The quadrivalent MenACWY conjugate vaccine is recommended in preference to the plain polysaccharide meningococcal vaccine for all age groups (B).
- Under 2-year-olds: if unimmunized or partially immunized, should receive MenC conjugate vaccine at 3 and 4 months of age, followed by the MenC conjugate vaccine (such as the Hib/MenC combination vaccine, Menitorix®) at 12 months as well as the quadrivalent MenACWY conjugate vaccine booster no earlier than 1 month later (B, C). An additional booster of Hib/MenC should be given at the second birthday.
- In infants at particular risk of non-C serotype infections consideration may be given to the use of conjugate MenACWY vaccine in place of MenC conjugate vaccine in the above schedule.
- Children aged ≥2 years and adults should receive one dose of a MenC conjugate vaccine (such as the Hib/MenC vaccine, Menitorix®) followed by a single dose of the quadrivalent MenACWY conjugate vaccine one month later, irrespective of their previous immunization status.

- Travellers to endemic areas should receive the quadrivalent MenACWY conjugate vaccine before travelling (B).

Influenza vaccination

- All patients should receive yearly influenza vaccination (B).

Antibiotic prophylaxis and treatment

The increased risk of infection in patients with an absent or non-functioning spleen is life-long but is highest early after splenectomy. As discussed above, most instances of serious infection are due to encapsulated bacteria, with pneumococcal disease being predominant. The impact of invasive pneumococcal disease and its high mortality has had a major influence on both vaccination and antibiotic strategies. Other more unusual infections are well described.

The use of life-long prophylactic antibiotics directed against pneumococcal disease has been BCSH policy for more than 20 years (BCSH, 1996). Penicillin prophylaxis is highly effective in children with sickle cell disease and this experience provides the main evidence for continuing prophylaxis in other at risk groups (Riddington & Owusu-Ofori, 2002;

Cummins *et al*, 1991.) Failures of both vaccination and antibiotic prophylaxis are well documented.

The risk of sepsis post-splenectomy is highest immediately post-operatively. However, cases of fulminant infection have been reported more than 20 years after splenectomy.

The risk is greatest in children up to the age of 16 years and in adults over 50 years (reviewed by William *et al*, 2007). Additional risk factors include surgery for haematological malignancy as opposed to trauma, poor or no response to pneumococcal vaccination and previous invasive pneumococcal disease (Eber *et al*, 1999; Cherif *et al*, 2006; Meerveld-Eggink *et al*, 2008). It is not certain how these individual risk factors are linked; however, it is clear that some patients are at much greater risk than others and that this information may be used in risk stratification.

The use of life-long penicillin prophylaxis has potential disadvantages as it can be associated with development of bacterial resistance, may have side effects including allergy and may be associated with poor adherence (Keenan *et al*, 1999).

High-risk groups (described below) need careful counselling and follow up to ensure adherence to antibiotic prophylaxis.

The available data supports the continued use of penicillin prophylaxis (or equivalent) in hyposplenic patients up to aged 16 years and those over 50 years. Patients who have inadequate responses to pneumococcal vaccination or who have had a previous episode of invasive pneumococcal disease remain at high risk and should continue prophylaxis indefinitely. After splenectomy for trauma the risk is greatest in the immediate post-operative period, and antibiotic prophylaxis should include this period at least (Malangoni *et al*, 1984). Patients treated for haematological malignancy, particularly those who have received splenic irradiation or who have ongoing GvHD are also at continuing high risk.

These factors enable some risk stratification, and those with lowest risk may choose to stop regular antibiotic prophylaxis. Some will choose to continue, and those with higher risk should be encouraged to continue indefinitely (Falletta *et al*, 1995; Keenan *et al*, 1999).

At the first indication of systemic infection (high fever) all patients have access to and should start urgent treatment with appropriate antibiotics, based on specific locally agreed protocols (although evidence is lacking). In patients taking prophylaxis treatment should be from an antibiotic class likely to be non-cross resistant. Choice of antibiotic should be made with regard to appropriate microbiological advice and local protocols.

Oral penicillins remain the prophylactic drugs of choice in areas with low pneumococcal resistance. Specialist microbiological advice should be sought where this is not the case or for travel abroad. In patients with confirmed penicillin allergy an appropriate macrolide may be substituted depending on local practice.

Recommendations

- **Life long prophylactic antibiotics should be offered to patients considered at continued high risk of pneumococcal infection (B, C).**
- **Factors associated with high risk of invasive pneumococcal disease in hyposplenism include: aged less than 16 years or greater than 50 years, inadequate serological response to pneumococcal vaccination, a history of previous invasive pneumococcal disease, and splenectomy for underlying haematological malignancy particularly in the context of on-going immunosuppression (B, C).**
- **Patients not at high risk should be counselled regarding the risks and benefits of lifelong antibiotics and may choose to continue or discontinue prophylaxis (C).**
- **All patients should carry a supply of appropriate antibiotics for emergency use (C).**
- **Patients developing symptoms and/or signs of infection, despite the above measures, must be given systemic antibiotics and admitted urgently to hospital (B, C).**

Research and audit

There is an unmet need for improved pneumococcal vaccines and prospective assessment of serological response to vaccination in hyposplenic and asplenic patients. Further definition of groups at high risk of invasive pneumococcal disease should allow improved targeted prophylactic strategies.

Regular audit should continue. Readily auditable areas include vaccination rates, adherence to antibiotic prophylaxis and the current outcome of severe infection in asplenic and hyposplenic patients (Kyaw *et al*, 2006; Lammers *et al*, 2010).

Conclusions

Infection in patients with an absent or dysfunctional spleen remains largely preventable. Preventative strategies continue to be based on education of staff and patients, appropriate immunization schedules and chemoprophylaxis.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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