Journal of Adolescent Health 59 (2016) S21–S28

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Review article

Treatment of Meningococcal Disease

Simon Nadel, M.B.B.S., M.R.C.P. *

Paediatric Intensive Care Unit, St. Mary's Hospital and Imperial College London, London, United Kingdom

Article history: Received November 12, 2015; Accepted April 18, 2016
Keywords: Meningococcal disease; Treatment; Children

A B S T R A C T

Meningococcal disease is a life-threatening infection that may progress rapidly, even after appropriate treatment has commenced. Early suspicion of the diagnosis is vital so that parenteral antibiotic treatment can be administered as soon as possible to reduce the complications of infection. The outcome of meningococcal disease is critically dependent on prompt recognition of two important complications: shock and raised intracranial pressure. Rapid recognition of disease and of these complications, together with appropriate management is crucial to the outcome of affected patients. This article summarizes the clinical features of invasive meningococcal disease, diagnostic tools, treatment modalities, and common post-infection sequelae.

Infection with the bacterial pathogen *Neisseria meningitidis* is the predominant cause of meningitis and septicemia globally [1,2]. Humans are the only reservoir for the bacterium, which resides primarily in the nasopharynx; colonization occurs in approximately 10% of adults and can increase to 24% during adolescence [3–5].

Prompt recognition of meningococcal infection and aggressive early treatment are of paramount importance in reducing mortality, which occurs in approximately 10% of those with invasive meningococcal disease (IMD), even with treatment, and can reach as high as 50% in those left untreated [6].

The rapid recognition of IMD is of critical importance to patient survival and outcomes. Understanding the signs of infection is particularly important in industrialized countries, such as the United States and United Kingdom, where disease rates are low and physicians will likely see few cases over the course of their practice. Prompt administration of effective parenteral antimicrobial therapy and early recognition and management of the complications of IMD, including shock and raised intracranial pressure (ICP), are critical to improving patient outcomes. This manuscript will review the clinical features of IMD, methodologies for identification of the bacterium, current treatment modalities, and post-infection sequelae.

Clinical Features of Invasive Meningococcal Disease

The initial onset of IMD follows the clinical course of a classic bacterial infection which may pose a challenge for the attending physician. Typically, a nonspecific febrile illness with chills, muscle aches, nausea, and vomiting may precede the development of more specific features of meningococcal infection, such as classic features of meningitis (e.g., headache, neck stiffness, photophobia, and altered mental state); however, less than a third of patients will present with this traditional "typical" diagnostic combination [5,7]. In approximately 40%–70% of patients with meningococcal disease, the nonspecific features will progress to sepsis due to meningococcal septicemia, with signs of circulatory insufficiency, shock, and the pathognomonic petechial/purpuric rash [8].

Meningitis and septicemia are the most common clinical features of IMD and each can occur independently or in

Conflicts of Interest: S. N. has served as a consultant for Pfizer Inc and Novartis.
Disclaimer: Publication of this article was supported by Pfizer, Inc. The opinions or views expressed in this supplement are those of the authors and do not necessarily represent the official position of the funder.

* Address correspondence to: Simon Nadel, M.B.B.S., M.R.C.P., St. Mary's Hospital and Imperial College London, Praed Street, London W21NY, United Kingdom.
E-mail address: s.nadel@imperial.ac.uk.

1054-139X/
http://dx.doi.org/10.1016/j.jadohealth.2016.04.013

combination [9]. The presence of a nonblanching hemorrhagic rash is pathognomonic of IMD and reflects coagulopathy. Coagulopathy is universal in severe sepsis regardless of the etiology, but the pathognomonic hemorrhagic rash is a distinguishing feature of IMD. The petechiae and purpura may occur anywhere on the body, so their presence with fever and signs of sepsis should automatically suggest IMD and prompt the initiation of immediate parenteral antimicrobial therapy. It should be noted that the classic rash may not be present until the disease is well advanced and may be atypical or absent in a significant proportion of IMD cases [9].

Shock is a consistent feature of meningococcal septicemia and is multifactorial in origin due to the consequence of several pathophysiologic processes, including endothelial cell dysfunction, myocardial dysfunction, altered vasomotor tone, and impaired cellular metabolism [10]. Shock occurs because perfusion of vital organs, such as the brain and heart, is maintained at the expense of perfusion of less vital organs (e.g., skin, kidneys, and gut). In the early phase of shock, vasoconstriction reduces blood flow to skin, peripheries, and certain organs, particularly the kidneys and gut, and patients usually present with cool peripheries, prolonged capillary refill time, and oliguria. It should be noted that children may have normal blood pressure until shock is advanced. In severe cases, focal ischemia of the skin or even whole limbs may occur as well as renal failure. Despite the presence of shock, brain perfusion and function is often relatively well preserved until the disease is far advanced, which can lead to an underestimation of the degree of cardiovascular collapse by less-experienced clinicians. Eventually, a decreased level of consciousness indicates loss of cerebral vascular autoregulation and reduced brain perfusion.

Septic shock can lead to and is the consequence of impaired myocardial function, the origin of which is multifactorial: hypovolemia leads to decreased cardiac filling; metabolic derangements (including hypoxia, acidosis, hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia, and hypoglycemia) lead to impaired myocardial contractility. In addition, bacterial products and inflammatory cytokines directly suppress myocardial contractility. Plasma interleukin-6 has been identified as a specific myocardial depressant factor in meningococcal septicemia [11]. Myocardial contractility may improve with volume resuscitation and correction of metabolic derangements, but patients with signs of ongoing shock despite adequate volume resuscitation require inotropic support to improve myocardial function.

The onset of hypotension signifies a failure of homeostatic mechanisms. It should be remembered that diagnosis of shock in children does not rely on the presence of systemic hypotension. Children may have normal blood pressure until shock is advanced.

Raised ICP occurs as a result of inflammation of the meninges and capillary leak in the brain, leading to cerebral edema. Most patients with meningococcal meningitis have mildly raised ICP, but significantly raised ICP is uncommon. Although most critically ill children with meningococcal infection have shock as their primary clinical problem, some present with meningitis and raised ICP as their predominant clinical manifestation. Signs of raised ICP include declining level of consciousness, focal neurologic signs (including unequal, dilated, or poorly responsive pupils; relative hypertension; and bradycardia), and papilledema (a late finding in acutely raised ICP).

Identification of Meningitis: Lumbar Puncture and Computed Tomographic Imaging

Lumbar puncture (LP) is a definitive diagnostic tool that can yield rapid microbiological confirmation of meningococcal meningitis and can exclude other causes of meningeal infection. In the absence of antibiotic treatment before assessment, LP detects meningococcus in 90% of meningitis-positive patients while blood cultures detect 40%–75% of cases [12]. It should be noted that antibiotic treatment before LP reduces the efficacy of bacterial detection by multiple methods (e.g., cerebrospinal fluid culture, polymerase chain reaction, latex agglutination) [13]. Although microbiological confirmation is important for establishing disease etiology, LP may be dangerous in the presence of raised ICP or shock because it may cause cerebral herniation or further cardiovascular compromise; consequently, this procedure should be avoided in the initial assessment of patients with clinically apparent meningococcal disease. Contraindications to LP include cardiorespiratory insufficiency, raised ICP (evidence for which includes fluctuating or deteriorating levels of consciousness [Glasgow Coma Score $\leq$ 8]; normal or high blood pressure in the presence of a slow or normal heart rate; unequal, dilated, or poorly reacting pupils; focal neurologic signs or abnormal posturing; seizures; and papilledema) and coagulopathy [14]. When LP is contraindicated, blood culture, polymerase chain reaction, urine antigen detection, skin biopsy, and serum inflammatory markers can be used to establish a diagnosis [13].

Computed tomographic brain imaging is frequently used in patients with a depressed level of consciousness and is particularly recommended where there is a broader differential diagnosis. However, cranial computed tomographic scanning is not a sensitive way of assessing ICP and cannot help in making the decision to perform an LP, which must be made on the basis of clinical assessment [14].

Treatment of Invasive Meningococcal Disease

Treatment guidelines have been developed over many years. These are regularly updated and are useful reminders of the management principles for infants, children, and young adults with meningococcal septicemia and meningitis, leading to substantial improvements in mortality (Figures 1–3). Recognition and management of shock and/or raised ICP is the priority in effective treatment of IMD. Early and aggressive fluid resuscitation is associated with improved survival in pediatric septic shock [15]. In the absence of shock, ICP can be treated with osmotherapy to reduce cerebral edema and improve brain perfusion.

In the newly diagnosed patient, parenteral antimicrobial therapy is a top priority and should be given as quickly as possible and certainly within 1 hour of recognition of IMD as recommended in the most recent national and international guidelines (Table 1) [14,16]. It should be noted that patients with IMD can transmit meningococci within the first 24 hours of antibiotic therapy, therefore, measures such as droplet precautions should be taken to minimize exposure to health care workers [17]. Antibiotic therapy rapidly reduces circulating plasma endotoxin levels in patients with IMD; increased endotoxin levels have been associated with severity of illness, including the presence of septic shock, multiple organ failure, and death in patients with IMD [18]. Even with antibiotic

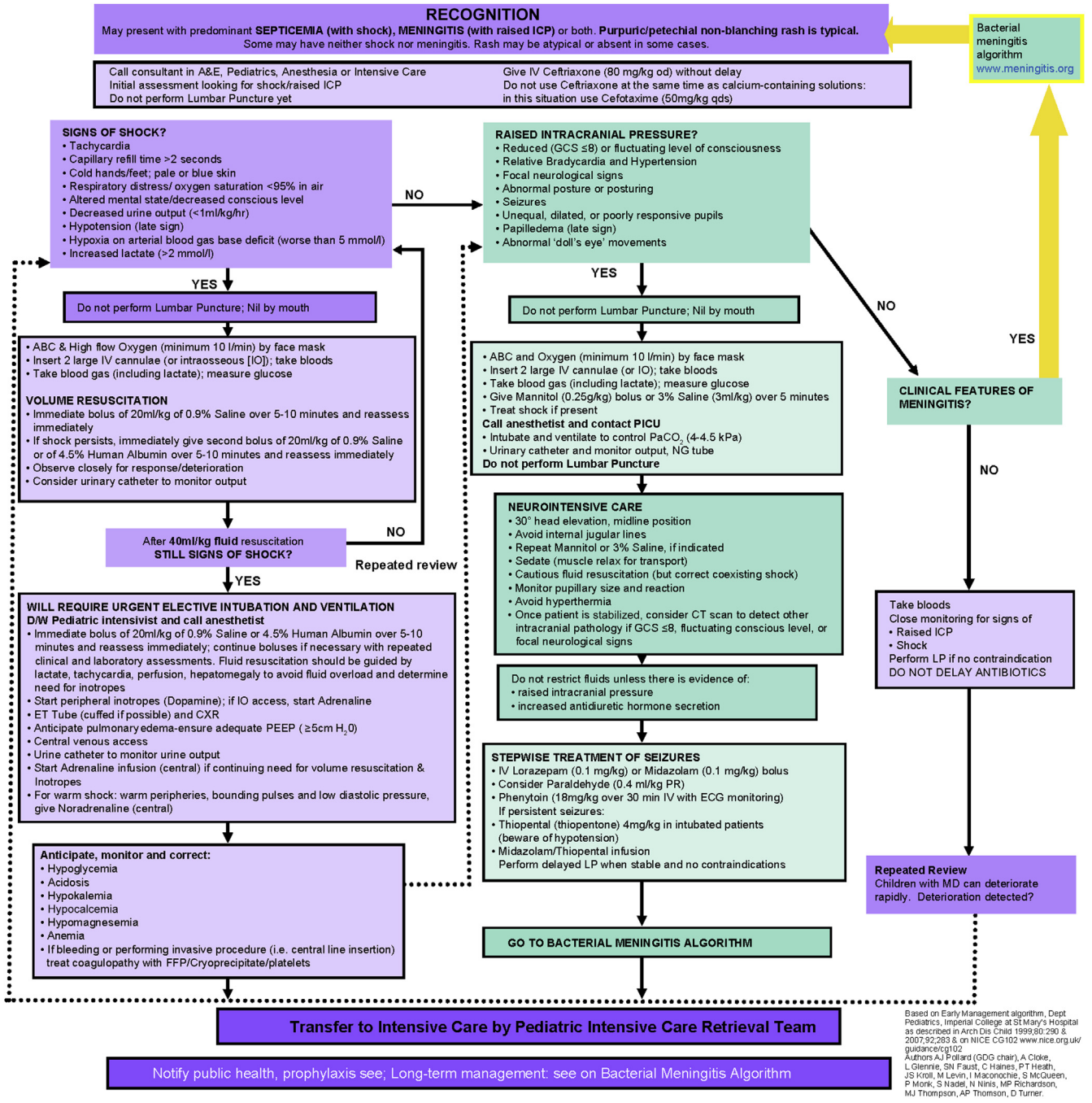

Figure 1. Management of meningococcal disease in children and young people. Eighth edition, incorporates NICE Bacterial Meningitis and Meningococcal Septicaemia Guideline CG102. Distributed in partnership with NICE. A&E = accident and emergency; ABC = airway, breathing, circulation; CT = computed tomography; CXR = chest x-ray; D/W = discuss with; ECG = electrocardiogram; ET = endotracheal; FFP = fresh frozen plasma; GCS = Glasgow Coma Scale; ICP = intracranial pressure; IO = intraosseous; IV = intravenous; LP = lumbar puncture; NICE = National Institute for Health and Care Excellence; NG = nasogastric; od = once daily; PEEP = positive end expiratory pressure; PICU = pediatric intensive care unit; PR = per rectum; qds = 4 times daily.

treatment, IMD carries a 10% mortality rate, but this is considerably lower than the 70%–85% mortality rate observed before the availability of antibiotics [19].

Cefotaxime, ceftriaxone, and penicillin are preferred as initial therapy in patients with a clinical diagnosis of IMD [17]. In a retrospective review of hospital records that included 381 patients with IMD, mortality was reduced by 40% when parenteral penicillin was administered before admission [20]. In the United States and United Kingdom, penicillin resistance is rare [17,21], and therefore, benzylpenicillin is the logical choice for urgent prehospital treatment. However, when penicillins are used, follow-up treatment with ceftriaxone, ciprofloxacin, or rifampin is necessary to eliminate nasopharyngeal carriage [17,19]. Chloramphenicol and meropenem can be used in cases of

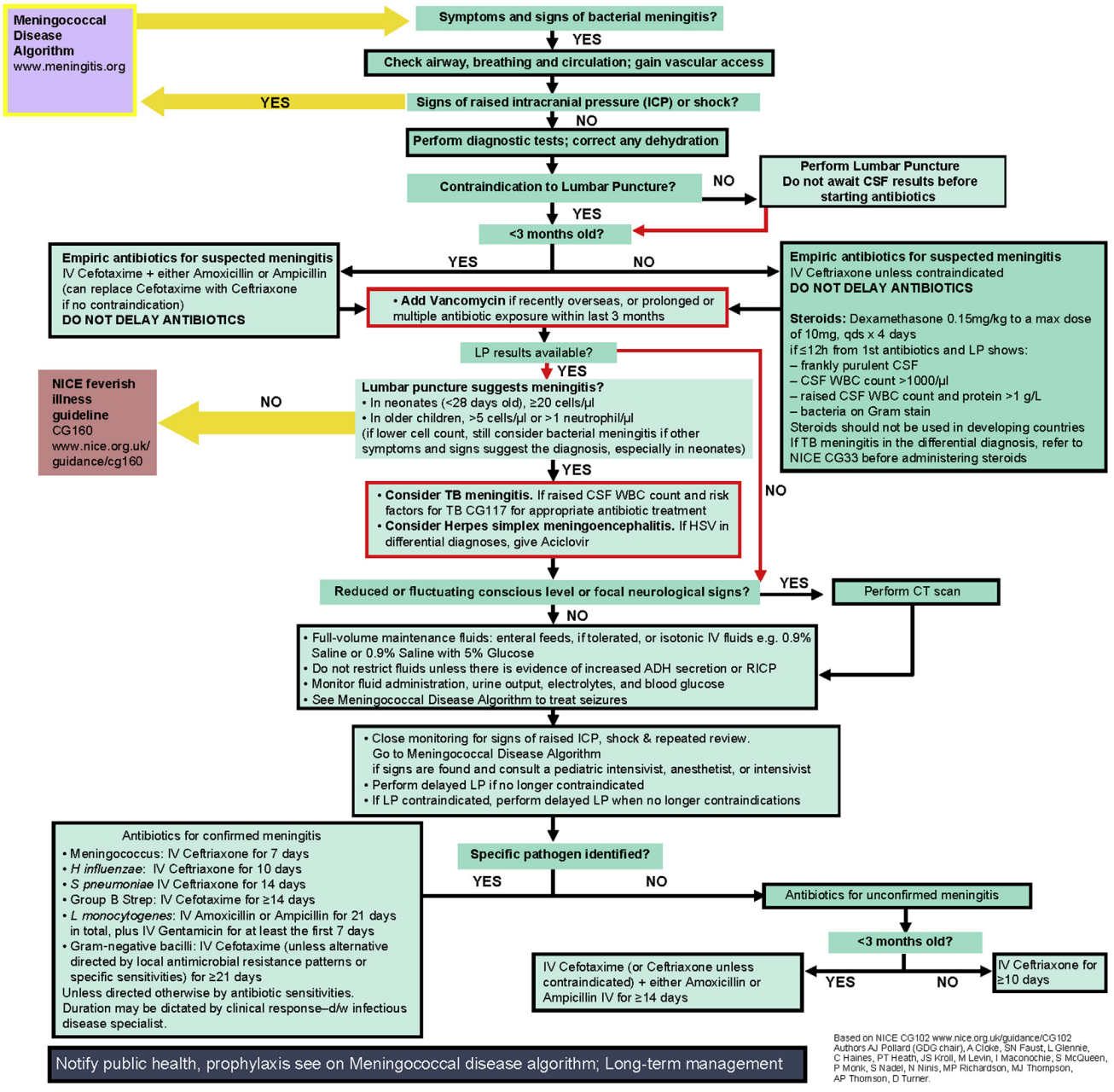

Figure 2. Management of bacterial meningitis in children and young people. Incorporates NICE Bacterial Meningitis and Meningococcal Septicaemia Guideline CG102. Distributed in partnership with NICE. ADH = antidiuretic hormone; CSF = cerebrospinal fluid; CT = computed tomography; HSV = herpes simplex virus; ICP = intracranial pressure; IV = intravenous; LP = lumbar puncture; NICE = National Institute of Health and Care Excellence; qds = 4 times daily; TB = tuberculosis; WBC = white blood cell.

penicillin allergy [17]. Empiric treatment with a third-generation cephalosporin is recommended in developed countries until a positive microbiological diagnosis is available, as there remains the possibility of either penicillin resistance or alternative diagnoses that might not be adequately treated by penicillin therapy alone. Other more rare infectious causes of purpura fulminans include *Streptococcus pneumoniae*, *Staphylococcus aureus*, or other gram-negative bacteria. The recommended duration of antibiotic therapy for IMD is a 5- to 7-day course of a third-generation cephalosporin for both meningococcal meningitis and septicemia [17].

Biochemical and Hematologic Derangements

Meningococcal septicemia often results in derangements in blood chemistry, including metabolic acidosis, hypoglycemia, hypocalcemia, hypokalemia, hypomagnesemia, or hypophosphatemia. Disseminated intravascular coagulation is common; there may be bleeding from mucosal surfaces and venipuncture sites. In addition, spontaneous pulmonary, gastric, or cerebral hemorrhage may occur. The skin may be severely compromised through inadequate perfusion as a result of vasoconstriction and coagulopathy. Decreased skin perfusion

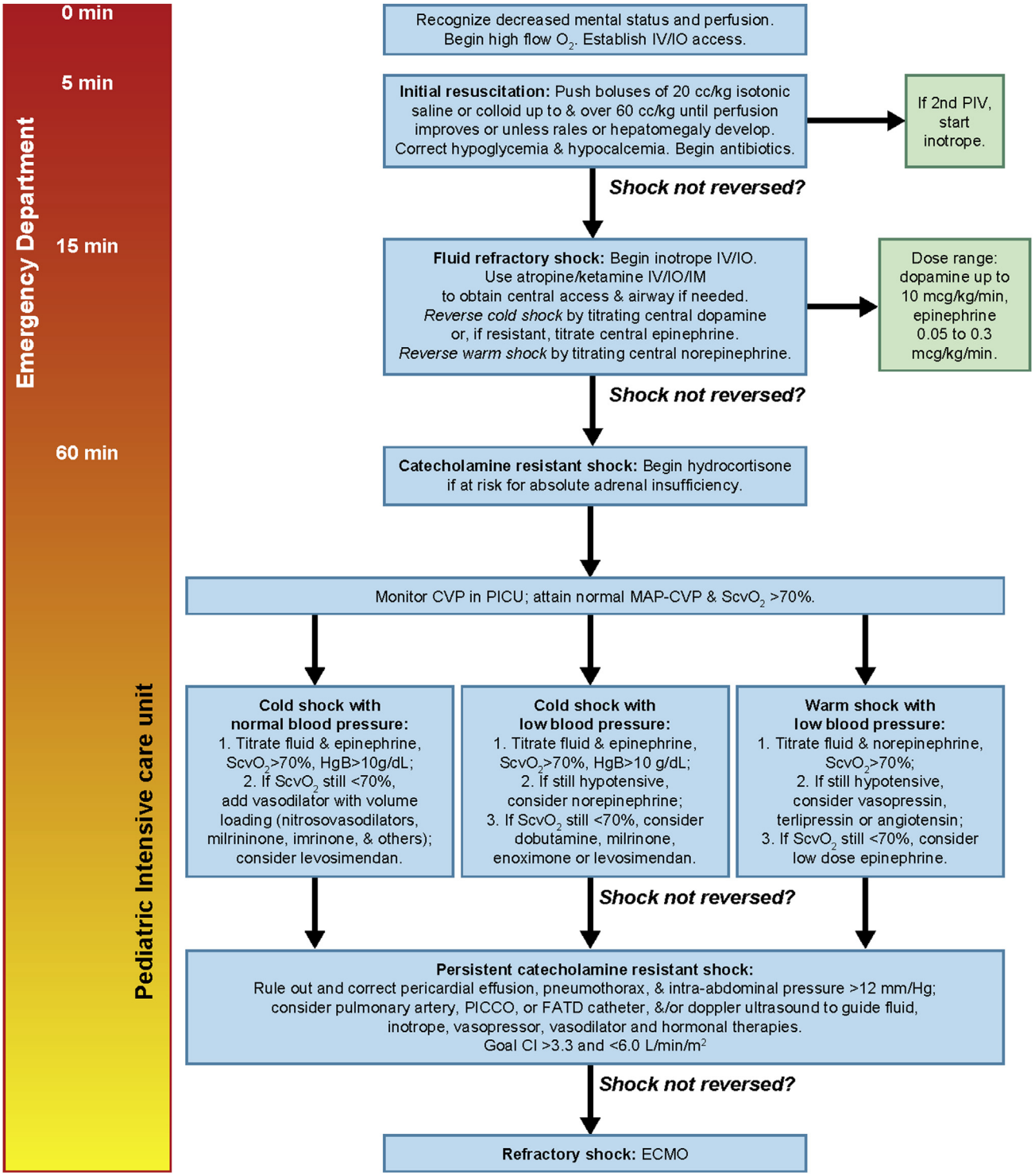

Figure 3. Algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in infants and children. CI = cardiac index; CRRT = continuous renal replacement therapy; CVP = central venous pressure; ECMO = extracorporeal membrane oxygenation; FATD = femoral arterial thermodilution; Hgb = hemoglobin; IM = intramuscular; IV = intravenous; IO = interosseous; MAP = mean arterial pressure; PICCO = pulse contour cardiac output; PICU = pediatric intensive care unit; PIV = peripheral intravenous; $ScvO_2$ = central venous oxygen saturation. Reproduced from Brierley J, Carcillo J, Choong K, et al.: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009; 37:666–688.

Table 1
Antibiotics and dosages used to treat meningococcal meningitis [35,36]

Antibiotic	Total daily dose	
	Children >1 month	Adults
Penicillin G	4×10^6 units, q 4 hours	4×10^6 units, q 4 hours
Ceftriaxone	50 mg/kg, q 12 hours	2 g, q 12 hours
Cefotaxime	50 mg/kg, q 6 hours	2 g, q 4–6 hours
Ceftazidime	50 mg/kg, q 8 hours	2 g, q 8 hours
Cefepime	2 g, q 12 hours	2 g, q 8–12 hours
Ampicillin	75 mg/kg, q 6 hours	2–3 g, q 4 hours
Nafcillin and oxacillin	50 mg/kg, q 6 hours	2 g, q 4 hours
Vancomycin	15 mg/kg, q 6 hours	10–15 mg/kg, q 8 hours
Gentamicin and tobramycin	2.5 mg/kg, q 8 hours	2 mg/kg, q 8 hours
Amikacin	10 mg/kg, q 8 hours	7.5 mg/kg, q 8 hours
Rifampin	6.7 mg/kg, q 8 hours	600 mg, q 24 hours
Meropenem[a,b]	40 mg/kg, q 8 hours	2 g, q 8 hours
Chloramphenicol[b]	50 mg/kg, qid 4 hours	50 mg/kg, qid 4 hours

q = every; qid = every day.
[a] Use restricted to >3 months of age.
[b] Use in the case of penicillin allergy.

may predispose pressure areas to ischemic damage, and tissue edema from capillary leak may cause compartment syndrome.

Prophylaxis of Close Contacts

Of special note, all individuals in close contact with an IMD-infected individual should receive chemoprophylaxis, regardless of previous meningococcal immunization. A number of antimicrobial agents are effective for chemoprophylaxis against *N. meningitidis* (Table 2) [17].

Adjunctive Therapies

Steroids given before or with the first dose of antibiotics appear to reduce the incidence of neurologic sequelae in *Haemophilus influenzae* type b meningitis and may be beneficial in pneumococcal meningitis [22]. There is also a reported trend of improved outcomes with steroid therapy in meningococcal meningitis [23]. Dexamethasone may be administered as adjunctive therapy in children aged ≥6 weeks with meningococcal meningitis, but the risk/benefit ratio needs to be considered, and dosing should occur before or concomitant with the first dose of antibiotics [24].

High-dose dexamethasone should be given in cases of suspected bacterial meningitis before (ideally within 4 hours), and no longer than 12 hours following, the first dose of parenteral antibiotics; a dose of .15 mg/kg 4 times per day for 2–4 days is recommended [14,25]. High-dose corticosteroid therapy is contraindicated in meningococcal septicemia with shock in the absence of meningitis because high-dose corticosteroids have been shown to worsen the outcomes of adults with septic shock [26].

There have only been two properly conducted, randomized controlled studies of other adjunctive therapies in IMD and one study examining a novel therapy for septic shock. In a randomized study of antiendotoxin antibody (HA-1A) conducted in children with meningococcal septicemia, no significant reduction in mortality was observed in children treated with HA-1A compared with placebo [27]. Subsequent studies in adults with gram-negative septicemia also showed no benefit of therapy with HA-1A [28]. In a randomized controlled trial of recombinant bactericidal permeability-increasing protein ($rBPI_{21}$), which binds and neutralizes endotoxin and blocks the inflammatory cascade, patients treated with $rBPI_{21}$ suffered fewer amputations, fewer blood product transfusions, and improved functional outcomes compared with those treated with placebo [29]. The study was not sufficiently powered to be able to detect a reduction in mortality [29]. This product is no longer available.

A randomized controlled trial of activated protein C was carried out in children with septic shock, with the primary end point being reduction in time to resolve respiratory, cardiovascular, and renal organ failure as surrogate indicators of mortality [30]. The study was terminated early because it was felt it would be unlikely to reach its primary end point, with suggestions of an unfavorable risk/benefit profile.

Post-Infection Sequelae

A myriad of long-term complications are associated with IMD, some of which are irreversible and disabling. Sequelae occur in 11%–19% of surviving IMD patients [17], and the most frequently reported conditions are chronic pain, skin scarring, and neurologic impairment. Other common complications include hearing impairment, visual impairment, motor defects, behavioral

Table 2
Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease

Drug	Dose	Duration	Efficacy (%)	Cautions
Rifampin				
<1 month	5 mg/kg, orally, every 12 hours	2 days		
≥1 month	10 mg/kg (maximum 600 mg), orally, every 12 hours	2 days	90–95	Can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses. Not recommended for pregnant women.
Ceftriaxone				
<15 years	125 mg, intramuscularly	Single dose	90–95	To decrease pain at injection site, dilute with 1% lidocaine.
≥15 years	250 mg, intramuscularly	Single dose	90–95	To decrease pain at injection site, dilute with 1% lidocaine.
Ciprofloxacin				
≥1 month	20 mg/kg (maximum 500 mg), orally	Single dose	90–95	
Azithromycin[a]	10 mg/kg (maximum 500 mg)	Single dose	90	Not recommended routinely. Equivalent to rifampin for eradication of *Neisseria meningitidis* from nasopharynx in one study

[a] Use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.
From American Academy of Pediatrics. Meningococcal Infections. In: Kimberlin D., Brady M.T., Jackson M.A., et al., eds. Red Book 2015. Elk Grove Village, IL: American Academy of Pediatrics; 2015:547-558.

problems, and seizures [31]. Other less frequent complications include septic arthritis, conjunctivitis, and chronic meningococcemia [17]. Hearing loss and amputations occur in approximately 3% of IMD cases [31].

Careful follow-up of patients with IMD should be routine. Hearing tests are recommended within 4 weeks of hospital discharge [14]. Orthopedic complications may be reported several years after the acute infection due to bone growth plate abnormalities and may need complex orthopedic procedures.

Multidisciplinary team involvement for amputation, limb-fitting, and rehabilitation are required in patents who suffer amputation. More recently psychological and psychiatric complications of IMD have become increasingly recognized in up to one third of survivors. [32]. These include post-traumatic stress disorder, anxiety, depression, and behavioral/educational abnormalities. Management may require psychiatric and psychological follow-up and intervention.

Post-infectious inflammatory syndrome occurs in approximately 6%–15% of individuals with IMD typically within 4–12 days of IMD onset [7]. Arthritis is the most common inflammatory pathology associated with this syndrome and results primarily from the accumulation of antigen-antibody complexes that contain bacterial polysaccharide [7]. Approximately 10% of IMD cases have some form of arthritic sequelae [33]. The most common type of post-infectious arthritis affects one joint, particularly the knee, elbow, or ankle [34]. However, multiple joint involvement can occur. Other sequelae characteristics of post-infectious inflammatory syndrome include vasculitis, pleuritis, pericarditis, iritis, and episcleritis [7]. Usually, treatment of these post-infectious complications requires symptomatic treatment with antipyretics or nonsteroidal anti-inflammatory agents. However, once ongoing infection has been excluded, steroid treatment may be required, and the prognosis of these complications is excellent.

Summary

IMD is a life-threatening infection with a rapid onset and progression, so that early detection and prompt initiation of parenteral antimicrobial therapy is paramount for optimizing patient outcomes. Once the pathognomonic hemorrhagic rash appears the diagnosis is immediately apparent, but establishing the precise etiology of disease is important so that appropriate public health procedures can be put into place as soon as possible. LP is a definitive diagnostic tool that should be used in cases where the cause of meningitis is uncertain and where there is no contraindication. Parenteral antibiotics should be administered within 1 hour of IMD recognition to reduce the level of circulating endotoxin, and this may prevent or forestall complications such as septic shock and raised ICP. Physicians should be aware of sequelae that can occur within days of IMD onset.

Acknowledgments

Editorial support was provided by Susan E. DeRocco, Ph.D., of Complete Healthcare Communications, LLC and was funded by Pfizer, Inc.

Funding Sources

This supplement was supported by Pfizer, Inc.

References

[1] Rosenstein NE, Perkins BA, Stephens DS, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894–901.
[2] Trotter CL, Ramsay ME. Vaccination against meningococcal disease in Europe: Review and recommendations for the use of conjugate vaccines. FEMS Microbiol Rev 2007;31:101–7.
[3] Christensen H, May M, Bowen L, et al. Meningococcal carriage by age: A systematic review and meta-analysis. Lancet Infect Dis 2010;10:853–61.
[4] Caugant DA, Hoiby EA, Magnus P, et al. Asymptomatic carriage of Neisseria meningitidis in a randomly sampled population. J Clin Microbiol 1994;32:323–30.
[5] Centers for Disease Control and Prevention. Meningococcal Disease. Available at: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/mening.pdf. Accessed October 30, 2015.
[6] World Health Organization. Meningococcal Meningitis Fact Sheet No 141. Available at: http://www.who.int/mediacentre/factsheets/fs141/en/#. Accessed August 13, 2015.
[7] Strelow VL, Vidal JE. Invasive meningococcal disease. Arq Neuropsiquiatr 2013;71:653–8.
[8] Thompson MJ, Ninis N, Perera R, et al. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367:397–403.
[9] Dwilow R, Fanella S. Invasive meningococcal disease in the 21st century-an update for the clinician. Curr Neurol Neurosci Rep 2015;15:2.
[10] Sinha R, Nadel S. Understanding shock. Paediatrics Child Health 2013;23:187–93.
[11] Pathan N, Hemingway CA, Alizadeh AA, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet 2004;363:203–9.
[12] Pollard AJ, Finn A. Neisseria meningitidis. In: Long SS, Pickering LK, Prober CG, eds. Principles and practice of pediatric infectious diseases, 4th ed. Philadelphia, PA: Saunders; 2012:730–41.
[13] Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 2010;23:467–92.
[14] National Insititute for Health and Care Excellence. Meningitis (bacterial) and menigococcal septicaemia in under 16s: Recognition, diagnosis and management. Available at: www.nice.org.uk/guidance/CG102. Accessed October 19, 2015.
[15] Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. JAMA 1991;266:1242–5.
[16] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637.
[17] American Academy of Pediatrics. Menigococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. Red book. Elk Grove Village, IL: American Academy of Pediatrics Committee on Infectious Diseases; 2015:547–58.
[18] Brandtzaeg P, Kierulf P, Gaustad P, et al. Plasma endotoxin as a predictor of multiple organ failure and death in systemic meningococcal disease. J Infect Dis 1989;159:195–204.
[19] Macneil J, Cohn A. Chapter 8: Meningococcal disease. VPD surveillance manual, 5th ed. Atlanta, GA: Centers for Disease Control and Prevention; 2011.
[20] Cartwright K, Reilly S, White D, et al. Early treatment with parenteral penicillin in meningococcal disease. BMJ 1992;305:143–7.
[21] Heath PT, Breathnach AS. Treatment of infections due to resistant organisms. Br Med Bull 2002;61:231–45.
[22] McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997;278:925–31.
[23] de Gans J, van de Beek D. European dexamethasone in adulthood bacterial meningitis study I. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549–56.
[24] Pneumococcal infections. In: Kimberlin D, Brady MT, Jackson MA, et al., eds. Red book. Elk Grove Village, IL: American Academy of Pediatrics Committee on Infectious Diseases; 2015:626–38.
[25] Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.
[26] Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: A meta-analysis. Crit Care Med 1995;23:1294–303.
[27] Derkx B, Wittes J, McCloskey R. Randomized, placebo-controlled trial of HA-1A, a human monoclonal antibody to endotoxin, in children with meningococcal septic shock. European Pediatric Meningococcal Septic Shock Trial Study Group. Clin Infect Dis 1999;28:770–7.
[28] Hurley JC. Towards clinical applications of anti-endotoxin antibodies; a re-appraisal of the disconnect. Toxins (Basel) 2013;5:2589–620.
[29] Levin M, Quint PA, Goldstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPI21) as adjunctive treatment for

children with severe meningococcal sepsis: A randomised trial. rBPI21 Meningococcal Sepsis Study Group. Lancet 2000;356:961–7.
[30] Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: A multicentre phase III randomised controlled trial. Lancet 2007;369:836–43.
[31] Pace D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. Vaccine 2012;30(Suppl. 2):B3–9.
[32] Garralda ME, Gledhill J, Nadel S, et al. Longer-term psychiatric adjustment of children and parents after meningococcal disease. Pediatr Crit Care Med 2009;10:675–80.
[33] Schaad UB. Arthritis in disease due to Neisseria meningitidis. Rev Infect Dis 1980;2:880–8.
[34] Goedvolk CA, von Rosenstiel IA, Bos AP. Immune complex associated complications in the subacute phase of meningococcal disease: Incidence and literature review. Arch Dis Child 2003;88:927–30.
[35] Greenlee JE. Acute bacterial meningitis. Merck manual, professional version. Rahway, NJ: Merck Publishing Group; 2015.
[36] Chloramphenicol Prescribing Information. Available at: http://www.drugs.com/pro/chloramphenicol-injection.html. Accessed May 20, 2016.