Recommendations for the management of pediatric septic shock in the first hour (part I)

Guillermo Kohn Loncarica, M.D.[a], *Ana Fustiñana, M.D.*[a] *and Roberto Jabornisky, M.D.*[b]

ABSTRACT
In the past two years, different organizations have updated their clinical practice guidelines for hemodynamic support in pediatric septic shock. The studies conducted in adults have questioned the initial management of sepsis in accordance to protocols based on achieving various goals. However, the usefulness of these protocols in children has been demonstrated. The possibility of adhering to guidelines may vary depending on patients and facilities, so it is necessary to update the general aspects of initial care for children with sepsis. The proposal is to shift the paradigm from an "individual practice guideline," which is universal for all, to an "institutional practice guideline" and to assess the factors that should be improved at each facility. This manuscript is divided into two parts. The first part analyzes the bundles for the early detection of septic shock. Part two addresses treatment, stabilization, referral, and process analysis.
Key words: *patient care bundles, septic shock, pediatrics, sepsis.*

http://dx.doi.org/10.5546/aap.2019.eng.e14

To cite: Kohn Loncarica G, Fustiñana A, Jabornisky R. Recommendations for the management of pediatric septic shock in the first hour (part I). *Arch Argent Pediatr* 2019;117(1):e14-e23.

a. Emergency Department, Hospital "Prof. Dr. Juan P. Garrahan," Autonomous City of Buenos Aires.
b. School of Medicine, Universidad Nacional del Nordeste, Corrientes. Argentina.

E-mail address:
Guillermo Kohn Loncarica, M.D.: gkohnloncarica@gmail.com

Funding:
None.

Conflict of interest:
None

Received: 11-18-2017
Accepted: 6-4-2018

GLOSSARY

CPG: clinical practice guideline.
ICU: intensive care unit.
IPG: institutional practice guideline.
SS: septic shock.

INTRODUCTION

Sepsis is one of the main causes of mortality in children worldwide; therefore, it is a top priority for the public health system.[1-4] It is caused by an inadequate immune response to an infection and is characterized by organ system failure, which is highly life-threatening.[5]

The 2017 World Health Assembly of the World Health Organization (WHO) approved Resolution 70.7, which urged Governments worldwide to strengthen sepsis-related policies and processes and recommended to reinforce health workers training aimed at recognizing and effectively treating it.[6]

In this regard, national and international scientific societies and institutions have developed several clinical practice guidelines (CPGs) for the management of pediatric sepsis.[7-17] These CPGs were based on the use of clinical goal-directed protocols and the early administration of time-sensitive treatment. In spite of the criticism of this strategy in adult studies, pediatric studies have demonstrated the importance of its implementation when dealing with this condition.[18-23]

However, a "strict and similar" implementation of CPGs in all patients and at all facilities does not always yield the same results. Most likely, due to non-adherence to current concepts on process management without consulting those who make decisions together with the patient.[24-27] Thus emerges the need to shift the paradigm of a universally applicable CPG, regardless of the context and aimed at making individual decisions. The new proposal is an approach based on the institutional processes of each facility that involves all health care actors.[17]

The objective of this study is to review the concepts of pediatric septic shock (SS) management as per the CPGs published in the past two years[14-17] and to try and raise awareness among health care teams so as to develop institutional guidelines that include bundles aimed at improving the quality of care provided to children with sepsis.

Due to the extension and importance of this topic, we have opted to divide the study in two publications. Part one proposes to design "patient care bundles" and analyzes the septic shock early detection bundle. Part two addresses treatment, stabilization, optimal referral, and the assessment of pediatric SS care processes.

IMPORTANCE OF HAVING AND USING CLINICAL PRACTICE GUIDELINES FOR CHILDREN WITH SEPSIS

Patient care processes imply interaction among people; therefore, the implementation of improvements necessarily involves them.

The Surviving Sepsis Campaign [SSC]: International Guidelines for Management of Sepsis and Septic Shock recommends the implementation of changes in processes and bundle adherence.[15] In addition, the American College of Critical Care Medicine (ACCM) points out the need to change from a pediatric SS care paradigm based on an individual CPG, focused on the treating physician, and for use in all settings to an institutional practice guideline (IPG) according to the facility's capability.[17]

For the development of an IPG, the entire health care team should be involved (from the emergency department, hospitalization ward, critical care unit, pharmacy, laboratory, hemotherapy, as well as pre-hospital practitioners and primary health care providers, etc.) to coordinate on a diagnosis and time-sensitive treatment. An IPG should establish early detection points and design institutional mechanisms that may trigger an early and effective treatment, stabilization, eventual transfer to a different facility, and assessment of process compliance.[17,25-28]

An example of such need for change is fluid administration. At tertiary care facilities, an insufficient fluid administration may result in a greater mortality and an extended length of stay for children with sepsis.[21,24-27] However, primary and secondary care facilities (where there is no respiratory support, infusion pumps or hemodynamic monitoring), results may be different. Fluid administration in children with dengue in the first hour demonstrated a 100 % survival; however, in children with malaria or severe anemia, it may be harmful.[29,30]

An obstacle in the implementation of CPGs is the scarce level of adherence in most hospital settings. Reaching 100 % adherence to these interventions requires different human interactions, whose failure should be detected and corrected. Thus, once IPGs are established, diagnostic and therapeutic measures known as "patient care bundles" should be developed for a better approach and control of established processes.[17,25-28]

The concept was introduced in 2001 by the Institute for Healthcare Improvement (IHI) to improve quality and minimize variations in critically-ill patient care. Patient care bundles include three to five evidence-based practices related to a health care process that should be performed collectively to achieve a synergistic result that improves care.[31] With other nosological entities, their implementation has been effective as a strategy to improve results compared to regular care.[32-34] In pediatrics, Han et al. observed that the implementation of bundles for the management of SS was associated with better outcomes.[35]

The ACCM expert group proposes to establish four "bundles" (early detection; immediate, time-sensitive resuscitation; stabilization with adequate monitoring; and a continuous measurement of processes and corrections of what was done) (*Figure 1*).[17]

The National Institute for Health and Care Excellence (NICE) does not suggest bundles but underlines that, at a specific time of SS care, trained health care providers should intervene (emergency physicians, intensivists or pediatric hospitalists), especially if the patient is not responding to treatment in the first hour.[14] One of the main reasons for SS care failure is the late referral to a facility with a higher level of care and/or for consultation with a specialist. For this reason, the suggestion is to include the timely referral or transfer bundle (*Figure 1*). This is called the "sepsis code" and is based on the rapid response team methodology, with teams trained in critically-ill patient care, which facilitates a fast approach and timely referral to facilities with a higher level of care.[36-38]

This means that, based on the IPGs developed among the different health care actors, bundles should be designed that would warrant SS screening, optimize an adequate treatment for children with suspected or confirmed SS, and decide on referral to a different facility, if necessary, and this would allow to assess processes for continuous improvement.[15,17] *Table 1* shows a comparison of the main aspects included in each bundle.[14,15,17]

RECOGNITION BUNDLE

Early detection of SS is critical to establish an optimal, time-sensitive treatment. To this end, it is necessary to have clinical criteria adequate to current definitions.

The terminology of SS has been modified and made more complex over the years. In 1991, the first definitions were made based on the paradigms of that time.[39] Recognizing its limitations, in 2001, a new consensus conference was held, which expanded diagnostic criteria.[40] In this line, in 2005, the conclusions of the International Consensus Conference on Pediatric Sepsis were published.[41]

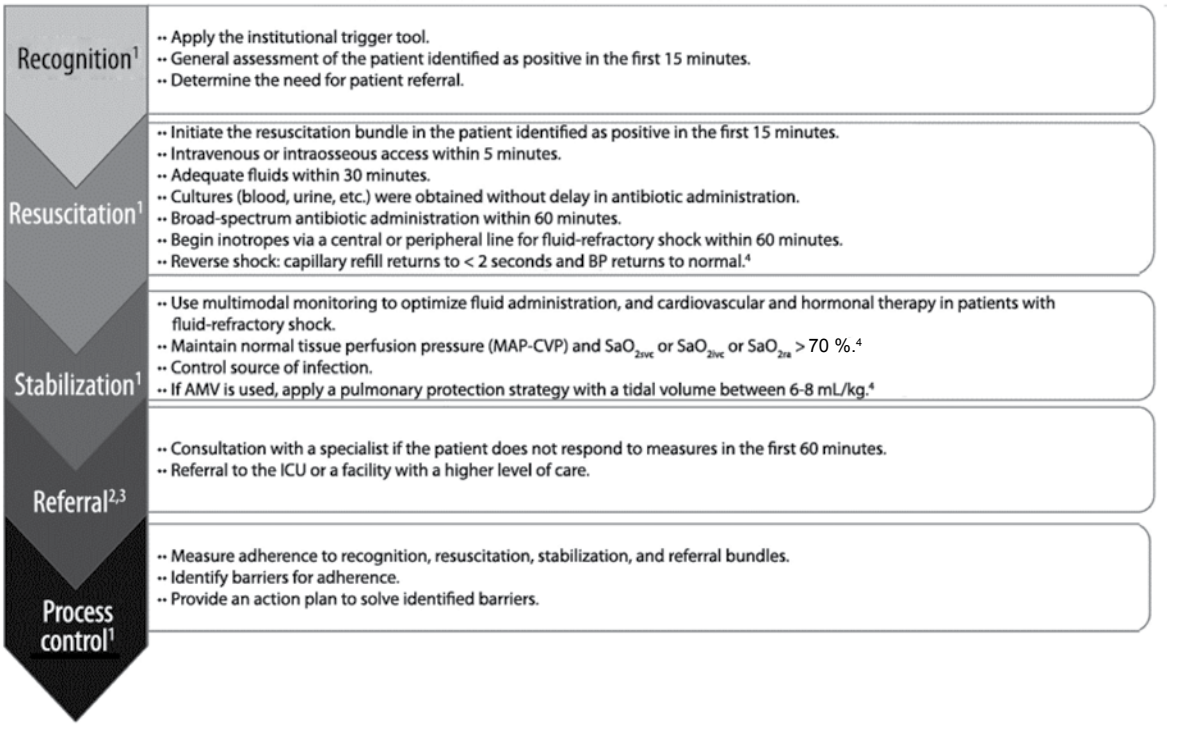
However, different studies have pointed out that patients outside the intensive care unit (ICU) experienced delays in early detection and, therefore, in their treatment and referral to the ICU.[42-45] Weiss et al. observed a moderate adherence to the consensus definitions in a study carried out in 26 countries.[46]

Therefore, there is a need to simplify sepsis detection criteria.[47,48] The new definitions only suggest the use of the terms "sepsis" and "septic shock."[5] Unlike what has been observed in adults, new criteria for children have not been published yet, although some authors have suggested to define sepsis as an infection plus tachycardia and tachypnea, and SS as sepsis accompanied by hypoperfusion.[49,50]

Angus et al. pointed out that the use of clinical criteria with accurate and strict cutoff points may not be effective when dealing with evolving, dynamic entities with inaccurate limits, such as SS.[51] The development of signs and symptoms that are not sufficiently clear should be considered in the first examination for an early detection. The simplification of diagnostic criteria allowed a prompt identification and a better survival of patients with SS.[18-20,30,52]

Fever, tachycardia, and vasodilation are common in children with benign infections.[17] Since these are non-specific signs and symptoms of sepsis, the NICE recommends to ask whether it may be sepsis in situations such as the following: a child who "feels very sick;" concern among family members or caregivers; a child shows changes in his/her regular behavior, is

FIGURE 1. *Pediatric septic shock bundles and elements for recognition, resuscitation, stabilization, referral, and process control*



BP: blood pressure; SaO_{2svc}: oxygen saturation in the superior vena cava; SaO_{2ivc}: oxygen saturation in the inferior vena cava; SaO_{2ra}: oxygen saturation in the right atrium; AMV: assisted mechanical ventilation; MAP: mean arterial pressure; CVP: central venous pressure; ICU: intensive care unit.

[1] Bundles suggested by the ACCM;[17] • [2] Process suggested by the NICE;[14] • [3] Obtained from the "sepsis code";[36-38]

[4] Bundles suggested by Han et al.[35]

irritable and/or cries inconsolably; consultations made by electronic means; and patients at risk (especially, infants and immunocompromised patients —receiving chemotherapy, corticosteroids or immunosupressors, with diabetes, splenectomized, and with sickle-cell disease—).[14] Initially, hemodynamic involvement may not be observed but tachypnea due to pulmonary involvement, oliguria due to renal involvement without hypoperfusion, etc. may be observed.[17] This may increase the number of assessed patients, but the associated expenses and mortality would be lower than not detecting sepsis in an early manner.[14]

TABLE 1. *Comparison of the main measures suggested by analyzed consensuses*

		Recently published consensuses		
Measures		**NICE guidelines[a]**	**Surviving Sepsis Campaign guidelines[b]**	**ACCM guidelines[c]**
General aspects	Population	✓ Neonates, children, adults (including obstetric patients).	✓ Adults.	✓ Neonates and children.
	Bundles	✓ No suggestions.	✓ Suggest institutional performance improvement programs. ✓ Mention bundles but do not provide details.	✓ Suggest the following bundles: ○ Recognition ○ Resuscitation ○ Stabilization ○ Institutional performance
Recognition	Detection tools	✓ Paediatric Sepsis Six.[d]	✓ Clinical criteria (heart rate, respiratory rate, blood pressure, etc.) and invasive or non-invasive monitoring.	✓ Septic shock trigger/identification tool.[e]
	Scores	✓ PEWS-POPS (do not recommend one).	✓ Not mentioned.	✓ Not mentioned.
	Clinical criteria	✓ They are divided into: ○ High risk ○ Moderate to high risk	✓ Based on signs and symptoms.	✓ Based on signs and symptoms proposed by the PALS.
Resuscitation	Strategy	✓ Goal-directed early therapy (not suggested or ruled out).	✓ Early therapy based on the hemodynamic profile.	✓ Goal-directed early therapy.
	Fluids	✓ An initial 20 mL/kg bolus followed by control for rales/liver ptosis up to 40-60 mL/kg, if necessary.	✓ An initial 30 mL/kg bolus followed by control for hemodynamic status.	✓ An initial 20 mL/kg bolus followed by control for rales/liver ptosis up to 40-60 mL/kg, if necessary.
	Vasoactive drugs	✓ Do not specifically recommend a drug.	✓ Prioritize noradrenaline.	✓ Prioritize noradrenaline (warm shock) and adrenaline over dopamine (cold shock). Support the use of a peripheral line.
	Monitoring	✓ Vital sign (heart rate, respiratory rate, blood pressure, etc.) and mental status (Glasgow or AVPU scale [alert, voice, pain, unresponsive]) monitoring.	✓ Vital sign monitoring (heart rate, respiratory rate, blood pressure, etc.) and invasive or non-invasive monitoring.	✓ Baseline clinical sign monitoring followed by multimodal monitoring.
Stabilization		✓ Not mentioned.	✓ Not mentioned.	✓ Multimodal monitoring and goals. ✓ Suggest the eradication of the source of infection and optimization of antibiotic therapy depending on the microorganism.
Referral		✓ Consultation with a specialist trained on making decisions in patients suspected of sepsis and with high risk criteria. ✓ Suggest the presence of trained staff if the patient does not respond to the initial treatment.	✓ Not mentioned.	✓ Not mentioned.
Process control		✓ Not mentioned.	✓ Not mentioned.	✓ Suggest to measure adherence to detection, resuscitation, and stabilization bundles. ✓ Suggest to identify barriers for adherence and provide an adequate plan to improve care.

[a] NICE: National Institute for Health and Care Excellence;[14] • [b] Surviving Sepsis Campaign guidelines (International);[15] • [c] ACCM: American College of Critical Care Medicine;[17] PALS: Pediatric Advanced Life Support –American Heart Association, USA–; PEWS: Paediatric Early Warning Score; POPS: Paediatric Observation Priority Score; • [d] Paediatric Sepsis Six;[66] • [e] Septic shock trigger/identification tool.[17]

If the foregoing is accompanied by tissue hypoperfusion (diminished or very far apart peripheral pulses, slowed down capillary refill –> 2-3 seconds– or flash capillary refill, cold, mottled or warm and vasodilated limbs, reduced urine output –< 1 mL/kg/h–, altered sensorium/somnolence, confusion, lethargy, etc.), SS should be considered with a greater mortality risk than sepsis.[14-17,30,52]

Hypotension is not necessary for the clinical diagnosis of SS, although its presence in a child with suspected infection is confirmatory.[8]

Children experience an initial stage of tachycardia without arterial hypotension (compensated shock). When compensation mechanisms are not enough to maintain a normal blood pressure, tachycardia and arterial hypotension occur (decompensated shock).[53]

Carcillo et al. reported that mortality was 5-7 % among children with compensated shock versus 30 % among those with decompensated shock. In addition, mortality in patients with tachycardia was 3 % and increased to 4.4 % if it was also associated with arterial hypotension, to 7.5 % if associated with capillary refill > 3 seconds, and to 27 % if associated with hypotension-related prolonged capillary refill. If these parameters were stabilized during the consultation, mortality reduced by 40 %.[54]

In children, SS is generally associated with profound hypovolemia and a good response to fluid administration.[8] Non-responsive children have variable hemodynamic patterns that need to be clinically identified. The most common pattern includes a low cardiac output and high peripheral resistance (cold shock). Its clinical manifestations include cold, mottled skin, slow capillary refill, weak pulses due to a small difference between systolic and diastolic blood pressure and, sometimes, a drop in blood pressure, which may lead to multiple organ dysfunction.

A smaller percentage of patients have high cardiac output and low peripheral resistance (warm shock). It is characterized by vasodilation, warm, red skin, bounding pulses due to a high difference between systolic and diastolic blood pressure, and shortened capillary refill time.[55]

In adolescents, it may present with a similar hemodynamic pattern as in adults (vasodilation due to vasomotor paralysis). If myocardial function is compromised, cardiac output is maintained through ventricular dilatation and tachycardia. The impossibility of maintaining ventricular dilatation or the presence of tachycardia have been associated with a worse outcome.[56]

SS clinical presentation models are associated with different entities. In children with community-acquired SS, cold shock would predominate, whereas in those with hospital-acquired SS, especially patients with central venous catheter-associated infections, warm shock would prevail.[57,58]

In spite of such historical representation (cold/warm), two-thirds of children may have hemodynamic profiles that differ from clinical examination signs.[59] Moreover, patients may shift from one clinical presentation to the other during treatment.[55]

Laboratory markers (lactic acid and troponin) do not provide the same evidence in pediatric SS compared to adult SS. The reviewed CPGs do not yet recommend their use in children.[14,16,17]

The NICE has pointed out that no sign or symptom itself is enough to diagnose sepsis or predict the patient's outcome.[14] On their own, they may over- or undervalue severity.[17] In addition, there is a wide variation between the thresholds reported in different studies for any sign or symptom.[14]

The Pre-Hospital Trauma Life Support (PHTLS) provides separate respiratory rates ranges for neonates up to 6 weeks, and for infants between 7 weeks and 1 year of age, but it does not establish ranges for adolescents over 16 years old. The WHO only provides respiratory rate ranges for children between 2 months to 5 years old (*Table 2*).

The Pediatric Advanced Life support (PALS) and the European Pediatric Life Support (EPLS) provide multiple ranges —ranges for awake children are tabulated. Likewise, they provide separate ranges for infants up to 3 months, and for those between 3 months and 2 years of age.

The PHTLS provides separate heart rate ranges for neonates up to 6 weeks, and for infants between 7 weeks and 1 year of age, but it does not establish ranges for adolescents over 16 years old (*Table 3*).

The ACCM suggests vital signs and ranges according to the PALS and the American Academy of Pediatrics' SS trigger/identification tool. It considers a heart rate > 205 to be "at risk" for neonates between 0 and 3 months old. It divides age groups into 10-13 years old and older than 13 years old. The signs of risk are heart rate > 100 beats per minute in both groups and respiratory rate > 30 per minute for children between 10 and 13 years old and 16 for

children older than 13 years (*Table 4*).

Multiple variable monitoring or multimodal monitoring (clinical, laboratory, invasive, non-invasive, etc.) enhances the determination of the underlying hemodynamic status.[14-17,59]

IN SUMMARY

All members of the health care team in contact with pediatric patients should be trained on the basic points for the detection of sepsis (*Table 5*).

At the emergency department or the

Table 2. *Normal respiratory rate (breaths per minute) thresholds by program*

	APLS/PHPLS	PALS	EPLS	PHTLS	ATLS	WHO
Neonates (< 1 month old)	30-40	30-60	30-40	30-50	< 60	---
0-1 year old	30-40	30-60	30-40	20-30	< 60	< 50
1-2 years old	25-35	24-40	26-34	20-30	< 40	< 40
2-3 years old	25-30	24-40	24-30	20-30	< 40	< 40
3-4 years old	25-30	24-40	24-30	20-30	< 35	< 40
4-5 years old	25-30	22-34	24-30	20-30	< 35	< 40
5-6 years old	20-25	22-34	20-24	20-30	< 35	---
6-12 years old	20-25	18-30	20-24	(12-20)-30	< 30	---
12-13 years old	15-20	18-30	12-20	(12-20)-30	< 30	---
13-18 years old	15-20	12-16	12-20	12-20	< 30	---

APLS: Advanced Pediatric Life Support; PHPLS: Pre-Hospital Pediatric Life Support; PALS: Pediatric Advanced Life Support; EPLS: European Pediatric Life Support; PHTLS: Pre-Hospital Trauma Life Support; ATLS: Advanced Trauma Life Support; WHO: World Health Organization.

Table 3. *Normal heart rate (beats per minute) thresholds by program*

	APLS/PHPLS	PALS	EPLS	PHTLS	WHO
Neonates (< 1 month old)	110-160	85-205	85-205	120-160	< 160
0-1 year old	110-160	100-190	100-190	80-140	< 160
1-2 years old	110-150	100-190	100-190	80-130	< 150
2-3 years old	95-140	60-140	60-140	80-120	< 150
3-5 years old	95-140	60-140	60-140	80-120	< 140
5-6 years old	80-120	60-140	60-140	80-120	< 140
6-10 years old	80-120	60-140	60-140	(60-80)-100	< 120
10-12 years old	80-120	60-100	60-100	(60-80)-100	< 120
12-13 years old	60-100	60-100	60-100	(60-80)-100	< 100
13-18 years old	60-100	60-100	60-100	60-100	< 100

APLS: Advanced Pediatric Life Support; PHPLS: Pre-Hospital Pediatric Life Support; PALS: Pediatric Advanced Life Support; EPLS: European Pediatric Life Support; PHTLS: Pre-Hospital Trauma Life Support; WHO: World Health Organization.

Table 4. *Risk signs according to different consensuses*

	2016 NICE guidelines[14]				2017 ACCM guidelines[17]	
	Respiratory rate (breaths per minute)		Heart rate (beats per minute)		Respiratory rate (breaths per minute)	Heart rate (beats per minute)
	High risk	Moderate to high risk	High risk	Moderate to high risk		
< 1 year old	> 60	50-59	> 160 or < 60	150-159	> 60	See reference
1-2 years old	> 50	40-49	> 150 or < 60	140-149	> 40	> 190
3-4 years old	> 40	30-39	> 140 or < 60	130-139	> 40	> 140
5 years old	> 29	24-28	> 130 or < 60	120-129	> 40	> 140
6-7 years old	> 27	24-27	> 120 or < 60	110-119	> 30	> 140
8-11 years old	> 25	22-24	> 115 or < 60	105-114	> 30	> 140
≥ 12 years old	> 25	21-24	> 130	91-130	> 16	> 100

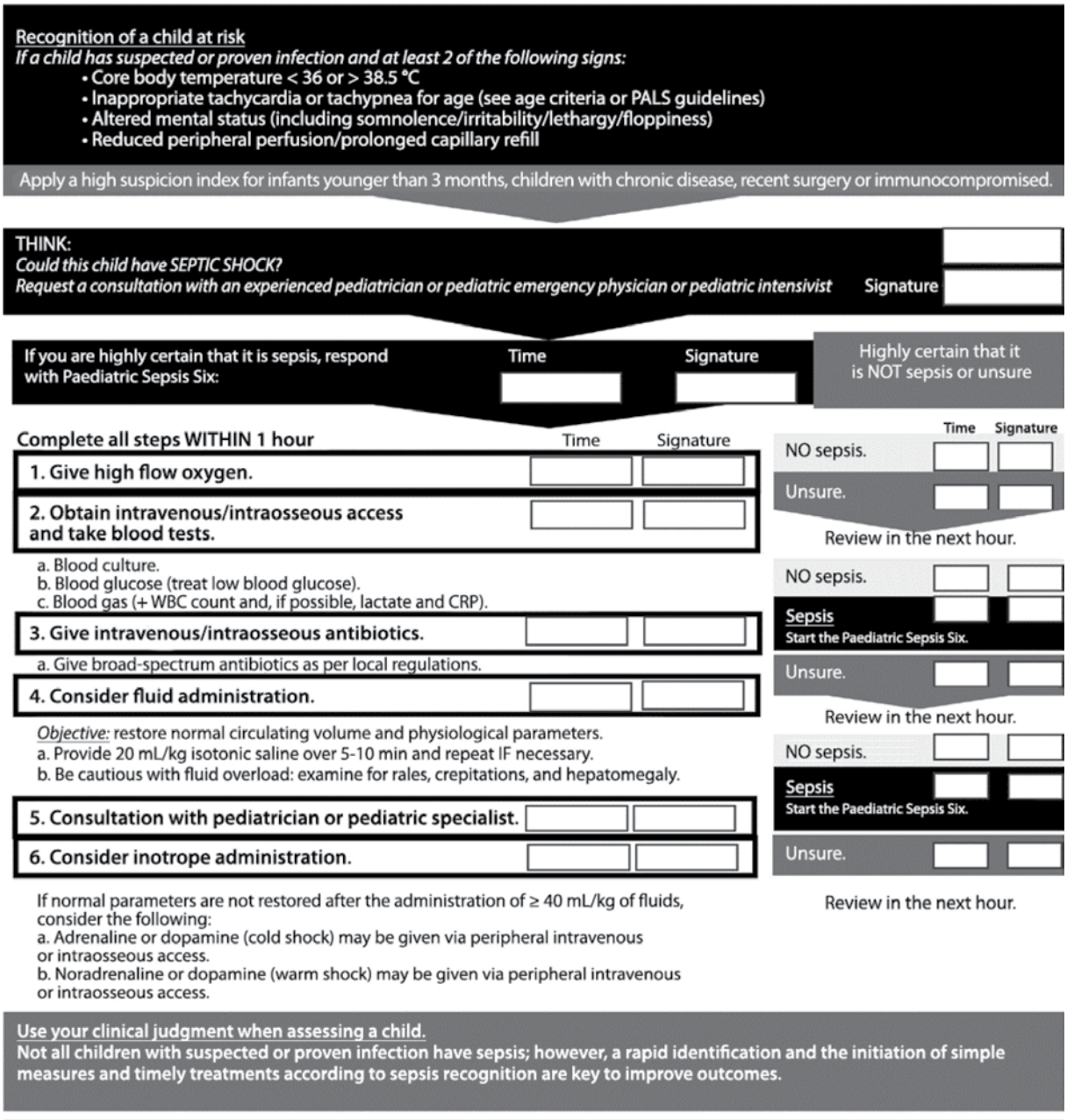
NICE: National Institute for Health and Care Excellence; ACCM: American College of Critical Care Medicine.

TABLE 5. *Clinical recognition of patients with sepsis and septic shock*

Term	Outcome measures
1. Sepsis	Infection + tachypnea + tachycardia (WITHOUT signs of hypoperfusion) + behavioral changes or malaise.
2. Septic shock	Infection + tachypnea + tachycardia (WITH signs of hypoperfusion).[a]
3. Compensated septic shock	Term 2 + normal blood pressure.
4. Decompensated septic shock	Term 2 + arterial hypotension.

[a] Signs of hypoperfusion: altered state of consciousness; diminished or very far apart –bounding– peripheral pulses; slowed down capillary refill –> 2-3 seconds– or flash capillary refill; cold or mottled limbs; reduced urine output: < 1 mL/kg/h.

FIGURE 2. *Paediatric Sepsis Six (adapted from the UK Sepsis Trust Paediatric Group)*



PALS: Pediatric Advanced Life support; WBCs: white blood cells; CRP: C-reactive protein.

hospitalization unit, outside the ICU, where the triage usually takes place, tools that trigger treatment-related actions once a patient is recognized as "positive" should be implemented (e.g., Paediatric Sepsis Six [PSS], Paediatric Early Warning Score [PEWS], Paediatric Observation Priority Score [POPS], etc.).[14,17,60-63]

Two recent studies adapted the quick Sequential Organ Failure Assessment (qSOFA) score, suggested by Sepsis-3, to pediatric values and compared it with other scores used at pediatric ICUs (PICUs). Although the Pediatric Sequential Organ Failure Assessment (pSOFA) showed an excellent intrahospital mortality discrimination capacity, consensuses do not recommend it yet[5,64,65] and, most likely, it may not be easily implemented at the emergency department.

At the PICU, in addition to basic criteria, multimodal monitoring findings may help for a better determination of hemodynamic status.[59]

The initial recognition bundle should include the following:

1) A trigger tool to identify clinical criteria (checklist, PSS, etc.) and populations at risk (immunocompromised and transplant patients, etc.).
2) A clinical assessment within 15 minutes for any patient identified as positive by the trigger tool.
3) Treatment trigger in the first 15 minutes.

Figure 2 describes an example of these measures according to the Paediatric Sepsis Six.[66] Measuring adherence will help to assess the performance of institutional teams.

CONCLUSION

Sepsis and SS are one of the main public health problems worldwide. Teamwork and the use of diagnostic and therapeutic bundles improve the management of sepsis and help to measure performance. Each facility should have a "recognition" bundle with their own tools to identify children with septic shock in an early manner. ■

REFERENCES

1. Watson RS, Carcillo Ja, Linde-Zwirble W, et al. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med*. 2003; 167(5):695-701.
2. Hartman ME, Linde-Zwirble WT, Angus DC, WatsonRS. Trends in the epideliology of pediaric severe sepsis. *Pediatr Crit Care Med*. 2013; 14(7):686-93.
3. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med*. 2007; 35(5):1244-50.
4. Kissoon N, Uyeki TM. Sepsis and the Global Burden of Disease in Children. *JAMA Pediatr*. 2016; 170(2):107-8.
5. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315(8):801-10.
6. Seventieth World Health Assembly. Improving the prevention, diagnosis and clinical management of sepsis. 2017; 70.7. [Accessed on: November 30th, 2017]. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R7-en.pdf.
7. Institute of Medicine. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academy Press. 2011. [Accessed on: November 30th, 2017]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK209538/?report=reader.
8. Carcillo JA, Fields AI, American College of Critical Care Medicine Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med*. 2002; 30(6):1365-78.
9. Group of Emergency Medicine, Chinese Pediatric Society, Chinese Medical Association; Group of Pediatrics, Chinese Society of Emergency Medicine, Chinese Medical Association; Editorial Board of Chinese Journal of Pediatrics. Recommended protocol for diagnosis and treatment of septic shock in children. *Zhonghua Er Ke Za Zhi*. 2006; 44(08):596-8.
10. Brierley J, Carcillo JA, 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(2):666-88.
11. Khilnani P, Singhi S, Lodha R, et al. Pediatric Sepsis Guidelines: Summary for resource-limited countries. *Indian J Crit Care Med*. 2010; 14(1):41-52.
12. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013; 39(2):165-228.
13. Subspecialty Group of Emergency Medicine, the Society of Pediatrics, Chinese Medical Association; Subspecialty Group of Pediatrics, the Society of Emergency Medicine, Chinese Medical Association; Pediatric Emergency Medicine Physicians, Chinese Medical Doctor Association. Expert consensus for the diagnosis and management of septic shock (infectious shock) in children (2015). *Zhonghua Er Ke Za Zhi*. 2015; 53(8):576-80.
14. National Institute for Health and Care Excellence. Sepsis: Recognition, Diagnosis and Early Management. London, 2016;51. [Accessed on: November 30th, 2017]. Available at: https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-management-pdf-1837508256709.
15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017; 43(3):304-77.
16. De Carlos Vicente JC. ¿Debemos adoptar nuevas recomendaciones en el manejo actual de la sepsis? *Rev Esp Pediatr*. 2017; 73(Supl 1):23-7.
17. Davis AL, Carcillo JA, Aneja RK, y et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med*. 2017; 45(6):1061-93.
18. ARISE Investigators; ANZICS Clinical Group, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014; 371(16):1496-506.
19. ProCESS Investigators, Yealy DM, Kellum JA, et al. A ran-

domized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014; 370(18):1683-93.
20. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal directed resuscitation for septic shock. *N Engl J Med*. 2015; 372(14):1301-11.
21. Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics*. 2003; 112(4):793-9.
22. Ventura AM, Shieh HH, Bousso A, et al. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. *Crit Care Med*. 2015; 43(11):2292-302.
23. De Oliveira CF, De Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med*. 2008; 34(6):1065-75.
24. Balamuth F, Weiss SL, Fitzgerald JC, et al. Protocolized Treatment Is Associated With Decreased Organ Dysfunction in Pediatric Severe Sepsis. *Pediatr Crit Care Med*. 2016; 17(9):817-22.
25. Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics*. 2011; 127(3):e758-66.
26. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics*. 2011; 127(6):e1585- 92.
27. Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS Sepsis Guidelines and Hospital Length of Stay. *Pediatrics*. 2012; 130(2):e273-80.
28. Paul R, Melendez E, Stack A, et al. Improving adherence to PALS septic shock guidelines. *Pediatrics*. 2014; 133(5):e1358-66.
29. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med*. 2005; 353(9):877-89.
30. Maitland K, Kiguli S, Opoka RO, et al. FEAST Trial Group: Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011; 364(26):2483-95.
31. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? *Curr Opin Infect Dis*. 2009; 22(2):159-66.
32. Resar R, Pronovost P, Haraden C, et al. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf*. 2005; 31(5):243-8.
33. Zilberberg MD, Shorr AF, Kollef MH. Implementing quality improvements in the intensive care unit: ventilator bundle as an example. *Crit Care Med*. 2009; 37(1):305-9.
34. Tanner J, Padley W, Assadian O, et al. Do surgical care bundles reduce the risk of surgical site infections in patients undergoing colorectal surgery? A systematic review and cohort meta-analysis of 8,515 patients. *Surgery*. 2015; 158(1):66-77.
35. Han YY, Carcillo JA, Espinosa V, Kissoon N. Quality improvement analysis of the global pediatric sepsis initiative registry simplified clinical bundle recommendations for industrialized developing and developed nations. *Pediatr Crit Care Med*. 2014; 15(Supple 4):15-6.
36. Syzek T. Code Sepsis: recognize, resuscitate, and refer. The Sullivan Group. [Accessed on: November 30th, 2017] Available at: http://blog.thesullivangroup.com/code-sepsis-recognize-resuscitate-and-refer
37. Jones C, Currie Cuyoy M, Jackson T. Code Sepsis: Rapid Identification and Treatment of Severe Sepsis in Floor Patients. *J Hosp Med*. 2013; 8 (Suppl 2). [Accessed on: November 30th, 2017]. Available at: http://www.shmabstracts.com/abstract/code-sepsis-rapid-identification-and-treatment-of-severe-sepsis-in-floor-patients/.
38. García-López L, Grau-Cerrato S, de Frutos-Soto A, et al. Impacto de la implantación de un Código Sepsis intrahospitalario en la prescripción de antibióticos y los resultados clínicos en una unidad de cuidados intensivos. *Med Intensiva (Madr Internet)*. 2017; 41(1):12-20.
39. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992; 20(6):864-74.
40. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003; 29(4):530-8.
41. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005; 6(1):2-8.
42. Umscheid CA, Betesh J, VanZandbergen C, et al. Development, Implementation and Impact of an Automated Early Warning and Response System for Sepsis. *J Hosp Med*. 2015; 10(1):26-31.
43. Whittaker SA, Mikkelsen ME, Gaieski DF, et al. Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. *Crit Care Med*. 2013; 41(4):945-53.
44. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: An analysis of outcomes for patients with onset on hospital wards versus intensive care units. *Crit Care Med*. 1998; 26(6):1020-4.
45. Sawyer AM, Deal EN, Labelle AJ, et al. Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. *Crit Care Med*. 2011; 39(3):469-73.
46. Weiss SL, Fitzgerald JC, Maffei FA, et al. Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Crit Care*. 2015; 19:325.
47. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013; 381(9868):774-5.
48. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315(8):762-74.
49. Carcillo J. Manejo del Shock Séptico. Jornadas Nacionales del Centenario de la Sociedad Argentina de Pediatría. Emergencias y Cuidados Críticos en Pediatría. 28-30 de abril de 2011. Buenos Aires, 2011. [Accessed on: November 30th, 2017]. Available at: http://www.sap.org.ar/docs/congresos/2011/eccri/3_1/audio.html.
50. Weiss SL, Deutschman CS. Are septic children really just "septic little adults"? *Intensive Care Med*. 2018; 44(3):392-4.
51. Angus D, Seymour C, Coopersmith CM, et al. Framework for the Development and Interpretation of Different Sepsis Definitions and Clinical Criteria. *Crit Care Med*. 2016; 44(3):e113-21.
52. Bang AT, Reddy HM, Deshmukh MD, et al. Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: effect of home-based neonatal care. *J Perinatol*. 2005; 25(Suppl 1):S92-107.
53. Kua J, Ong G, Ng KC. Physiologically-guided Balanced Resuscitation: An Evidence-based Approach for Acute Fluid Management in Paediatric Major Trauma. *Ann Acad Med Singapore*. 2014; 43(12):595-604.
54. Carcillo J, Kuch B, Han YY, et al. Mortality and functional morbidity after use of PALS/APLS by community physi-

cians. *Pediatrics*. 2009; 124(2):500-8.
55. Ceneviva G, Paschall J, Maffei F, Carcillo JA. Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics*. 1998; 102(2):e19.
56. Parker MM, Shelhamer JH, Natanson C, et al. Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: Heart rate as an early predictor of prognosis. *Crit Care Med.* 1987; 15(10):923-9.
57. Brierley J, Peters MJ. Distinct Hemodynamic Patterns of Septic Shock at Presentation to Pediatric Intensive Care. *Pediatrics*. 2008; 122(4):752-9.
58. Deep A, Goonasekera CD, Wang Y, Brierley J. Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. *Intensive Care Med*. 2013; 39(9):1602-9.
59. Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: A pilot observational study. *Pediatr Crit Care Med*. 2014; 15(15):e17-26.
60. Beitler JR, Link N, Bails DB, et al. Reduction in hospital-wide mortality after implementation of a rapid response team: a long- term cohort study. *Crit Care.* 2011; 15(6):R 269.
61. Akre AM, Finkelstein M, Erickson M, et al. Sensitivity of the Pediatric Early Warning Score to Identify Patient Deterioration. *Pediatrics.* 2010; 125(4):e763-9.
62. Sebat F, Musthafa A, Johnson D, et al. Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. *Crit Care Med*. 2007; 35(11):2568-75.
63. Oglesby KJ, Durham L, Welch J, Subbe CP. "Score to Door Time", a benchmarking tool for rapid response systems: a pilot multi-centre service evaluation. *Crit Care*. 2011; 15(4):R180.
64. Matics T, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3. Definitions in Critically Ill Children. *JAMA Pediatrics*. 2017; 171(10):e172352.
65. Schlapbach LJ, Straney L, Bellomo R, et al. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. *Intensive Care Med.* 2018; 44(2):179-88.
66. Tong J, Plunkett A, Daniels R. G218(P) The Paediatrict sepsis 6 initiative. *Arch Dis Child.* 2014; 99(Suppl 1):A93.