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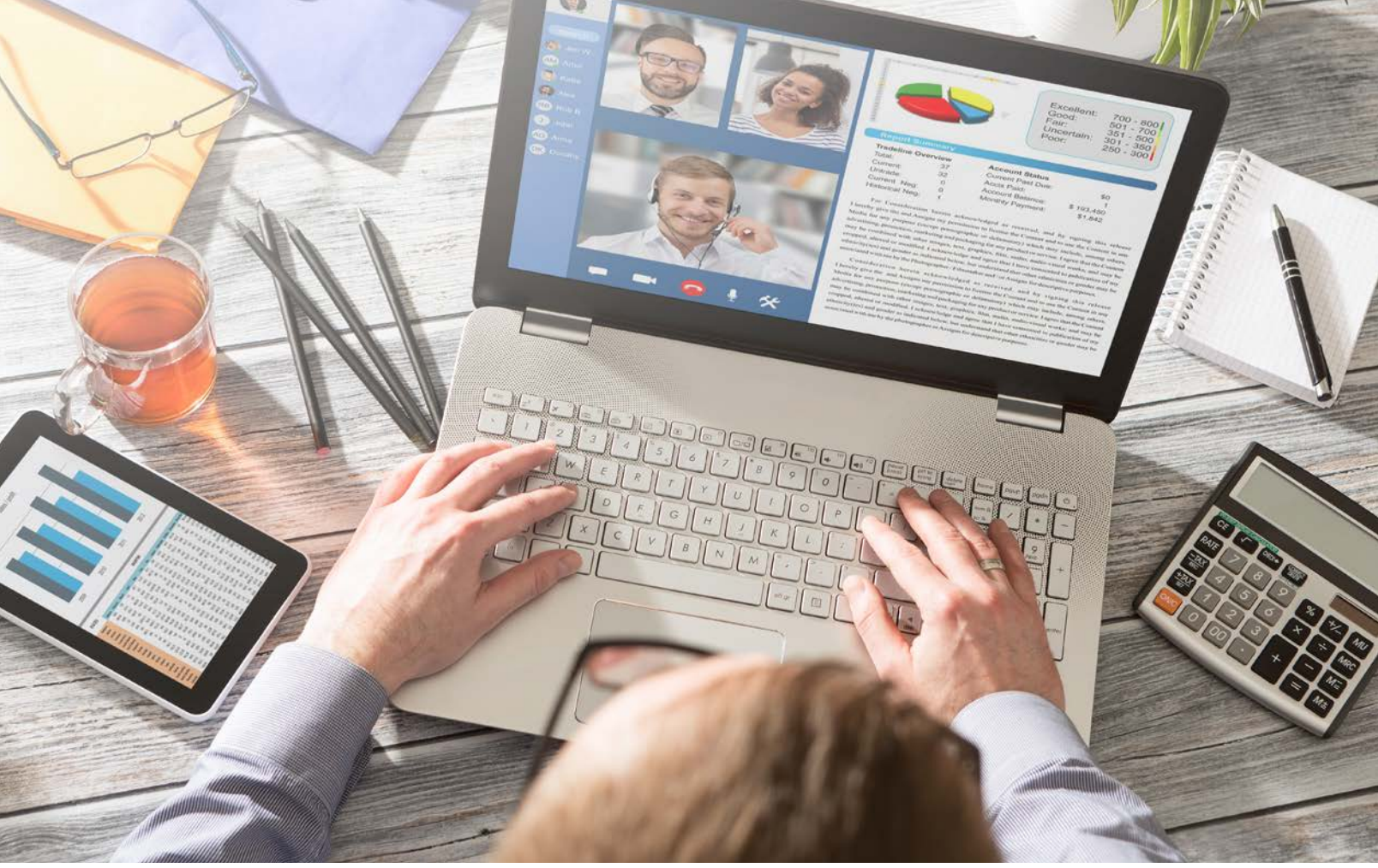

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by DYLAN DOMINGUEZ [1]; CHRIS SCHACH, MD

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A 17-year-old girl presents with a chief complaint of "maskne." The rash has been present for four months and has been peeling, red, and irritated. The patient reports that she wears a protective face mask most of the day and finds that her condition worsens with mask usage and improves with discontinuation. Examination shows grouped 1-2 mm erythematous papules, a few pustules, xerosis, and scaling in a perioral, perinasal, and periocular distribution.

What is the most likely diagnosis and appropriate intervention?

A. Allergic contact dermatitis due to her mask and/or facial cosmetic products. Apply topical 2.5% hydrocortisone cream BID, use a white cotton mask, and discontinue cosmetic products.

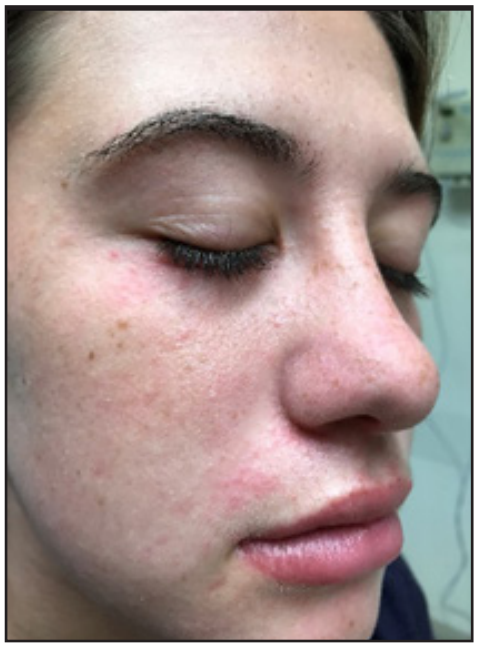
B. Acne worsened by mask usage (acne mechanica). Begin minocycline 100mg QD and tretinoin 0.01% gel QHS for six-eight weeks.

C. Seborrheic dermatitis exacerbated by mask usage. Start ketoconazole cream mixed equally with hydrocortisone 2.5% cream and applied BID for seven days, then as needed.

D. Perioral dermatitis induced or exacerbated by mask usage. Begin clindamycin 1% lotion applied BID and oral minocycline 100mg QD for 6-8 weeks.

E. Rosacea induced or exacerbated by mask usage. Prescribe metronidazole 0.75% gel applied BID and oral minocycline 100mg QD for 6-8 weeks.

Answer: D. The patient is experiencing perioral dermatitis (POD), also known as periorificial dermatitis, which was likely induced and exacerbated by prolonged periods of occlusion by her face mask. The colloquial term “maskne” (mask induced acne) popularized during the COVID-19 pandemic, refers to an acneiform facial eruption initiated or perpetuated by friction, moisture, warmth, and occlusion. Environmental and mechanical forces can induce or worsen a number of



facial dermatoses, such that “maskne” is not limited to an underlying diagnosis of acne.

Although the etiology of POD is unknown, the condition is thought to be multifactorial based on genetic, environmental, and hormonal factors. Possible pathways that lead to the development of POD include skin barrier impairment, atopic diathesis, and altered cutaneous microbiota.

Perioral dermatitis is predominately seen in young women, aged 20-45, though cases in men and children have been reported. It is most often noted around the mouth but may also involve perinasal and periocular skin (thus, the alternative designation “periorificial dermatitis”). POD shares some overlapping clinical features with rosacea, acne, atopic dermatitis, and seborrheic dermatitis. POD classically is characterized by the presence of grouped 1 – 2 mm inflammatory papules or papulopustules on an erythematous, slightly scaly base, clustered in the typical distribution. Stinging or burning sensations are common complaints. In the case presented, the involvement of the periocular are more consistent with POD, as mechanically induced acne (“acne mechanica”) generally spares this area. Acne is also characterized by the presence of comedones as well as generally larger papules and pustules. Perioral dermatitis is sometimes induced or exacerbated using inhaled corticosteroids, and topical corticosteroids should be avoided when managing this condition. Topical corticosteroids may initially result in improvement but will perpetuate the condition and, upon discontinuation, result in a “steroid rebound.” Some studies have suggested that colonization with Candida albicans, fusiform bacteria, or Demodex mites may play an etiologic role, but unlike seborrheic dermatitis, Malassezia yeast has not been implicated.

Potential cleansing and cosmetic irritants should be minimized, and soap-less cleansers and bland emollients recommended. Topical preparations containing metronidazole, erythromycin, sulfur preparations, azelaic acid, tacrolimus and pimecrolimus may be prescribed. More persistent disease may require oral agents, such as doxycycline, and some females respond to oral contraceptives. Isotretinoin has been used in recalcitrant cases.

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Diagnosis of Cystic Fibrosis in the Era of Newborn Screening

Case Report

Until screening of newborns for cystic fibrosis (CFNBS) became available, diagnosis of cystic fibrosis (CF) relied on recognition of classical signs and symptoms. Widespread use of CFNBS and prenatal screening have resulted in diagnosis of CF early in life before symptoms are recognized.[1] On the other hand, there is a growing subset of individuals who did not undergo CFNBS and are receiving a diagnosis of CF during adulthood. This has been partially attributed to increased awareness of CF disease heterogeneity among physicians, widespread availability of cystic fibrosis transmembrane conductance regulator (CFTR) genotyping, and updated diagnostic criteria.[2] The CF Foundation Patient Registry reported that, in 2017, only 58.4% of 880 new CF patients were diagnosed via CFNBS.[3] However, symptomatic diagnosis of CF can be challenging due to subtle symptoms and incomplete clinical presentation. In individuals with residual function CFTR mutations, clinical manifestations of CF may develop later in life.[1,2] Here we report four individuals who were diagnosed with CF symptomatically by pediatric pulmonologists at Arkansas Children's Hospital. Except for one patient, they were all born in the U.S., and none of them underwent CFNBS. Although each of them had symptoms suggestive of CF, their diagnoses were delayed.

Case1

An 11-year-old male presented to the emergency department with respiratory failure requiring intubation and mechanical ventilation. He had been treated for asthma and had moderate obstructive pattern in his spirometry. He also had a history of nasal polypectomy at 7 and 11 years of age. His sweat chloride was found to be 101 and 108 mmol/L Cl- and CFTR mutations were F508del /F508del. His fecal elastase level was 20 ug/g, consistent with pancreatic insufficiency (PI). His initial BMI was <10th percentile and he required G tube placement. His respiratory cultures were positive for P. aeruginosa, and after treatment his best FEV1 improved to 70% of predicted values.

Case 2

A 15-year-old female of Chinese descent was referred to the pulmonary clinic for recurrent sinus infections and chronic cough started at 5 years of age. The teen was born in China and the family migrated to the U.S. as a toddler.

When she was seen in the pulmonary clinic, her FEV1 was at 74% of predicted, and her chest imaging showed mild bronchiectasis. CF diagnosis was confirmed with a sweat Cl- test (77/73 mmol/L). She had normal pancreatic function. She had rare homozygous p.S492F mutations (this mutation has not been reported before). Since she was symptomatic and her respiratory cultures grew P aeruginosa, she was admitted to the hospital for IV antibiotic treatment. Following treatment, her best FEV1 remained in the mid 80% of predicted values. Unfortunately, the family did not want to accept the diagnosis of CF, which resulted in poor adherence to medications and clinical appointments.

Case 3

A 19-year-old, Caucasian female presented with chronic cough unresponsive to inhaled corticosteroids. She worked as a pharmacy technician at a commercial pharmacy and was well known to have daily "wet coughs." She also had a history of recurrent pneumonia and sinus infections. She described loose stools since infancy, although her admission BMI was at 24. Her initial FEV1 was 73% of predicted and her sweat Cl- was 109/101 mmol/L on two occasions. She was found to be homozygous F508del with mutations and she had pancreatic insufficiency. Her respiratory cultures were positive for P. aeruginosa and after treatment, her FEV1 improved to mid-80% of predicted values.

Case 4

A 14-year-old, Caucasian male presented with chronic cough that had worsened over time. He had abnormal chest imaging showing diffuse bronchiectasis. His chronic cough had been attributed to asthma for years. His nutritional status was poor, with a BMI at the 10th percentile on presentation. He had significant clubbing and diffuse crackles on his chest exam.

Diagnosis of CF was confirmed with sweat Cl- levels of 101 and 93.6. mmol/L. He was homozygous F508del with pancreatic insufficiency. His initial respiratory cultures were positive for P aeruginosa, and his initial FEV1 was 36% of predicted. Following hospitalization and institution of CF targeted treatment, his best FEV1 improved to mid-50% of predicted.

As seen in cases above, clinicians who are not experienced in CF likely expect that each CF patient should be presenting with failure to thrive, oily stools, barrel chest, clubbing, etc., (one size fits all). However, some CF patients may present with subtle symptoms and findings and

diagnosis of CF may be delayed. Sometimes, CF diagnosis may be delayed despite classical symptoms, significant lung disease, and pancreatic insufficiency. In addition, clinicians may have a less suspicion of CF since CFNBS is practiced extensively. This article will discuss CFTR mutations, genotype and phenotype relationship, and modulators of CFTR gene expression. Then, briefly CFNBS will be reviewed.

CFTR Mutations and Disease Heterogeneity in CF

Currently, there are more than 2000 CFTR mutations described; however, only 85% of the identified genetic variants are associated with the disease (www.cftr2.org). CFTR mutations are classified into five classes according to their effects on molecular mechanism and functional CFTR protein production.[4] Class I-III mutations result in either no CFTR protein production, truncated protein that is destroyed before reaching the cell membrane, or non-functional protein at the cell surface. In class IV and V mutations, while full length CFTR is located at the cell surface, either its conductance or amount would be insufficient.[5] Since there will be some functioning CFTR protein at the cell surface, Class IV and V mutations are mild mutations associated with pancreatic sufficiency. Recently, the Clinical and Functional Translation of CFTR initiative (www.CFTR2.org) was established to determine the clinical and functional impact of various CFTR mutations.

Genotype-phenotype Relationship and Modifiers of CFTR Function

The heterogeneity of the CF phenotype within the same mutation suggests that there are more factors involved in the determination of clinical phenotype than CFTR genotype alone. Although class I-III CFTR mutations are associated with pancreatic insufficiency and significant lung disease, individuals with these mutations show a high degree of variability in disease severity, complications, and survival.[4] For example, the F508del mutation, the most common CFTR mutation, is mostly associated with severe clinical phenotype. However, observations have shown that F508del phenotype can be variable, even in the same family and between siblings.

A recent Canadian report showed that 362 individuals received a diagnosis of CF as adults between 1990 and 2014. Median age at the diagnosis was 34.3 years, and these individuals had milder disease. Around 5% of 362 individuals were found to be homozygous for the F508del mutation, highlighting the heterogeneity in phenotype for this genotype.[2] Variability in CF lung disease even among siblings who have identical mutations was supported by a study of a pair of dizygotic twins with compound CFTR genotypes.[5] Although both twins had pancreatic insufficiency, the severity of the pulmonary disease varied considerably: while one twin had chronic P. aeruginosa infection with significant lung disease, the other twin had normal lung functions without chronic respiratory infection.[5] A European twin study demonstrated that monozygotic twins had a significantly higher concordance in severity of lung disease than did dizygotic twins, suggesting a strong genetic contribution to variability in severity of CF lung disease. A U.S. twins study also confirmed these observations, as long as twins lived in the same environment.[5]

Researchers have investigated several genes with respect to pulmonary CF disease modifiers. These potential gene modifiers include polymorphism in the promoter region of the tumor necrosis factor α gene, polymorphism in the transforming growth factor β gene, and variant alleles of mannose binding lectin.5 Functional CFTR gene expression is controlled by transcriptional, post-transcriptional, translational and post-translational regulatory mechanisms. Therefore, CFTR gene expression can also be modulated through mechanisms such as epigenetic changes that also may influence CFTR expression in different tissues.[6]

Although CF prevalence varies in different ethnicities, it should be noted that no ethnic group is protected from the disease.[7] CF is quite rare in Asian populations, and an epidemiological study of the Japanese population found the incidence of CF to be about 1 in 350,000. In China, there are no epidemiological statistics regarding incidence of this disease and there have been only 36 cases reported today, excluding our patient (case #2).[8] Since CF is extremely rare in Chinese individuals, our patient's parents refused to acknowledge that their child had CF.

CF Diagnosis

Arkansas initiated CFNBS in July 2017. By 2010, all 50 states and the District of Columbia had passed legislation requiring that all newborns be screened for CF. Although there are differences between countries and even in the U.S. regarding CFNBS protocols, there are essentially three steps (tiers) involved:

- **IRT:** Measuring immunoreactive trypsinogen (IRT) level from Guthrie cards is the first step of CFNBS. IRT screening is performed by state health departments; if this initial screening is abnormal, then the second tier is proceeded.[7]
- **DNA Mutation Analysis:** Most CFNBS protocols utilize analysis of a panel of CF-causing mutations based on the population genetics. If this limited panel identifies at least one CFTR mutation, then the screening is considered "positive" and infants are subjected to sweat chloride testing.
- **Sweat chloride testing:** Following the positive CFNBS, infants undergo sweat testing at CF Foundation accredited laboratories. Although molecular analysis of CFTR gene is useful in confirming the diagnosis, quantitative analysis of sweat Cl- concentration has been the gold standard for the diagnosis of CF.[1,7] CF is diagnosed when sweat Cl- level is > 60 mmol/L. Until recently, negative sweat Cl- concentration cut off level was different between adults and infants: Negative sweat Cl- level was <30 mmol/L in infants up to 6 months of age and <40mmol/L in individuals >6months old (22). In 2017, CFF consensus guideline has changed the definition of negative sweat test to Cl- levels <30 mmol/L in any age group. [1,7]

Table 1: Demographics and Clinical Features of Individuals Diagnosed with CF Symptomatically Late in Life

Case	Diagnosis Prior to CF	Age of Dx (years)	Ethnicity	CFTR Mutation	Sweat Cl Level	Initial Presentation	Pancreas Status	FEV1 at Diagnosis
#1	Asthma, Nasal polyps	11	Caucasian	Homozygous F508del (pPhe508del)	101/108 Mmol/L	Respiratory failure, nutritional failure	Insufficient	N/A Respiratory failure
#2	Asthma	15	Chinese	Homozygous p.S492F	77/73 Mmol/L	Cough, recurrent sinus infection	Sufficient	74%p
#3	Recurrent pneumonia, Sinusitis, Asthma	19	Caucasian	Homozygous F508del (pPhe508del)	109/101 Mmol/L	Cough, sputum production, GI symptoms	Insufficient	73%p
#4	Chronic cough	14	Caucasian	Homozygous F508del (pPhe508del)	93/101 Mmol/L	Respiratory distress, chronic cough, poor nutrition	Insufficient	36%p

Terminology

In attempts to differentiate the wide-spectrum clinical CF phenotypes, there have been various definitions proposed, including severe CF, mild CF, atypical CF, or classic/non-classic CF. In addition, there have been new/evolving definitions related to CFNBS, such as CFTR-related metabolic syndrome referring to inconclusive diagnosis following CFNBS (in the U.S.) and CF screen positive, an inconclusive diagnosis (in Europe). Finally, CFTR-related disorder refers to an entity with single organ/system involvement such as congenital bilateral absence of the vas deferens, pancreatitis, or bronchiectasis associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF[1,9]

False Negative Screening

CFNBS is complex and is not perfect; therefore, false negative results may occur. There are many potential reasons for a false negative screening including, but not limited to, unacceptable specimen quality, specimen labeling errors, and inappropriate testing cutoff value. Therefore, clinicians should be aware that a child can have CF despite negative NBS.10

Conclusion

CF diagnosis can be challenging in non-screened and screened populations. Severity of CF symptoms may be different even in siblings with the same CFTR mutations. Since nationwide CFNBS was implemented only recently in the U.S. and many individuals born prior to 2010 have not been screened, CF should be considered in individuals who present with symptoms suggestive of the disease. CFNBS is complex and is not perfect. Even after a negative screening, clinicians should maintain a high index of suspicion of CF. The terminology related to CFNBS is confusing and clinicians should work with CF specialists to communicate with their families after positive screening.

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by MATTHEW P. MALONE, MD [1]; ABDALLAH DALABIH, MD [1]; RONALD C. SANDERS JR., MD, MS [1]; MICHAEL H. STROUD, MD [1]

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Pediatric Sepsis: Update on Recognition and Management from the Surviving Sepsis Campaign

Abstract

Sepsis in children is increasingly common and is associated with high morbidity and mortality. In February 2020, international critical care experts published the first edition of "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children." Definitions were simplified to decrease confusion for clinical providers, and individual centers were encouraged to establish septic shock recognition and resuscitation "bundles," enabling timely triage and management of pediatric sepsis. Key features include: immediate IV/IO access, antibiotic administration within one hour, obtaining blood cultures, prompt fluid resuscitation with emphasis on frequent reassessment, and early initiation of inotropes.

Introduction

The International Society of Critical Care Medicine convened this year to provide updates on several subjects, including the revised Surviving Sepsis Campaign (SSC) guidelines for adults and children. A panel of 49 experts and 12 international organizations reviewed the most recent literature and shared their experience and expertise to establish the latest guidelines for pediatric septic shock and sepsis-associated organ dysfunction in children.[1] Intended users of these guidelines are health professionals caring for children in a hospital, emergency department, or other acute-care settings.

Sepsis remains a health concern for children, with more than 1.2 million annual cases worldwide. Mortality of sepsis in children varies depending upon associated risk factors, severity of illness, and geographic location of the patient, ranging from 4-50%.[1] Given the rural nature of much of Arkansas, the majority of patients with sepsis initially present to our frontline health care providers in urgent-visit centers, primary care offices, and emergency departments. Thus, this update is pertinent to all practitioners caring for children in Arkansas.

Background

Sepsis is a significant problem in the U.S. and accounts for over 40,000 deaths

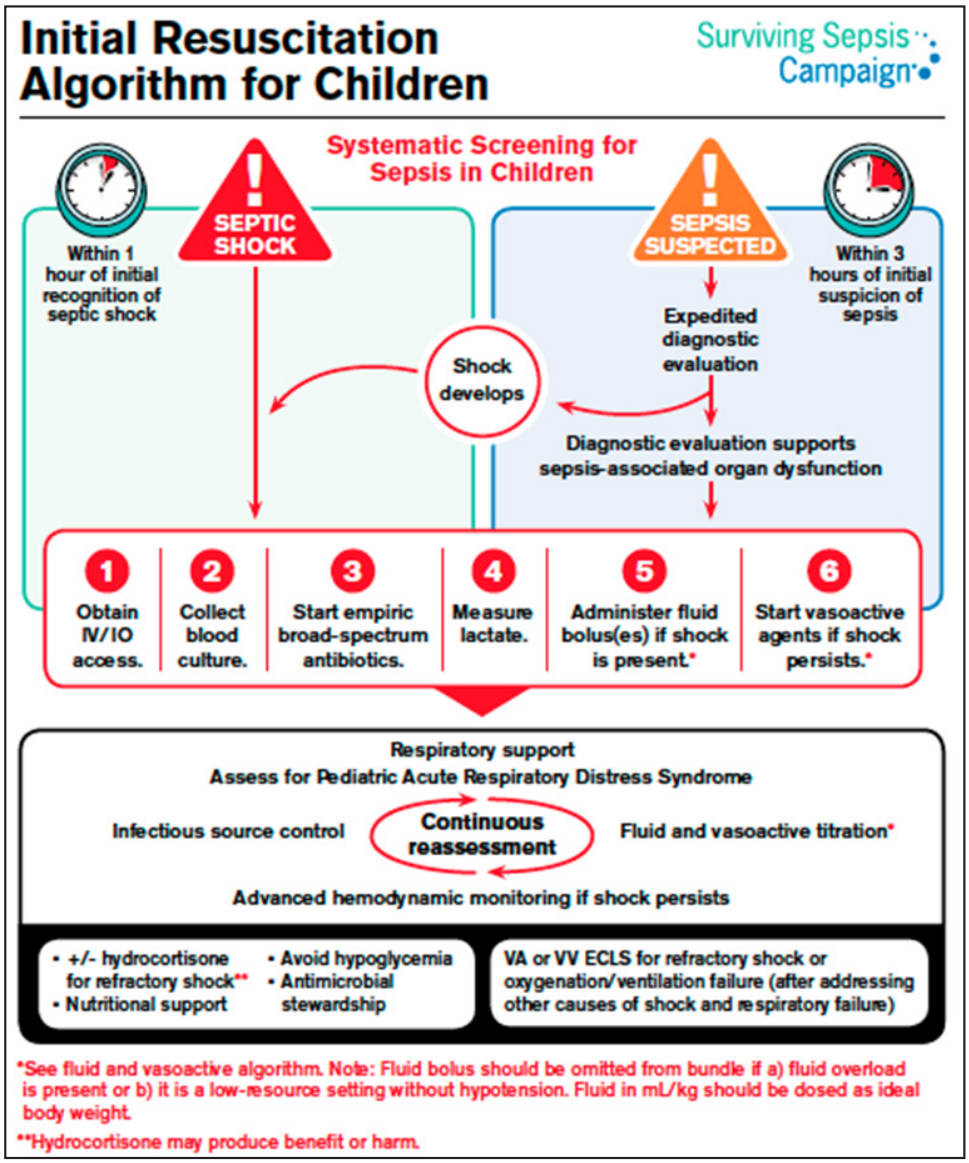

Figure 1. Initial Resuscitation Algorithm for Children. (Source: Surviving Sepsis Campaign. www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients)

per year (12.6 deaths per 100,000 population).[2] In a review of prospectively collected data from 43 U.S. children's hospitals from 2004 to 2012, pediatric severe sepsis was identified in over 49,000 cases, with an associated mortality of 14.4%. Severe sepsis affects slightly more males (53%), with a mean age of 7 years. Infants less than 1 year of age had the highest mortality (31.5%), followed by children 1-4 years of age (23.7%). The most common pediatric co-morbidities associated with mortality included cardiovascular (36.9%), neurologic (22.7%), and malignancy (22.3%).[3]

Diagnosis

Septic shock is a clinical diagnosis. Various definitions of sepsis and septic shock have evolved over time. The 2005 International Pediatric Sepsis Consensus Conference established definitions for sepsis, severe sepsis, and septic shock. These guidelines apply to children from full-term to 18 years of age. Sepsis can be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Severe sepsis is defined as a) systemic inflammatory response syndrome (SIRS), b) confirmed or suspected invasive infection, and c) cardiovascular dysfunction or acute respiratory distress syndrome (ARDS), or ≥ 2 non-cardiovascular organ system dysfunctions. Septic shock occurs in a subset of patients with sepsis and manifests as cardiovascular dysfunction leading to a) hypotension, b) treatment with vasoactive medication, and/or c) impaired end-organ perfusion4 (see Table 1).

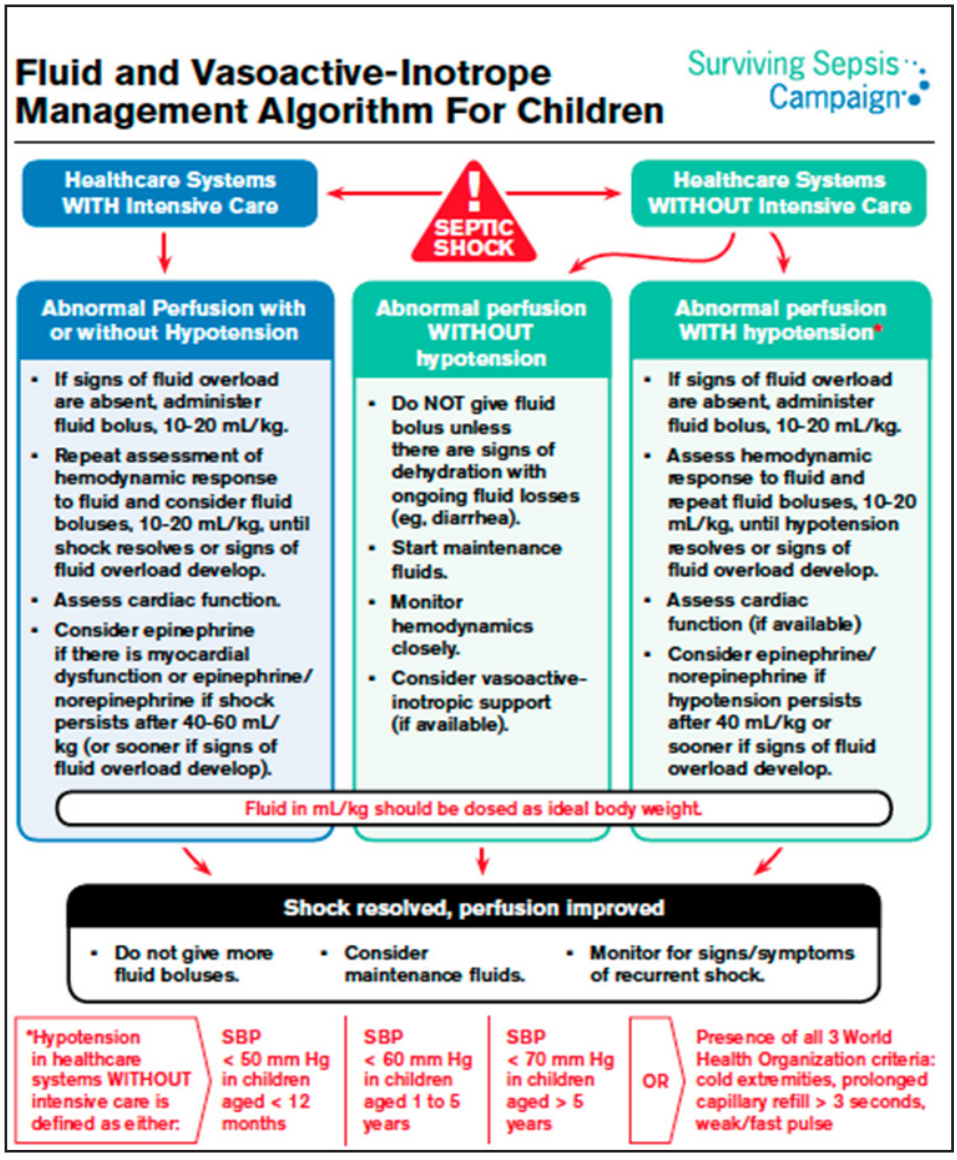

Figure 2. Fluid and Vasoactive-Inotrope Management Algorithm for Children. (Source: Surviving Sepsis Campaign. www.sccm.org/SurvivingSepsisCampaign/Guidelines/Pediatric-Patients)

In the updated 2020 pediatric sepsis guidelines from the Society of Critical Care Medicine, septic shock is defined as severe infection leading to cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion), and sepsis-associated organ dysfunction as severe infection leading to cardiovascular and/or non-cardiovascular organ dysfunction.[1] These new definitions were established to prevent potentially confusing classifications of sepsis, severe sepsis, and septic shock.

The recent update also added a broader pediatric age range: infants from 37 weeks' gestation to 18 years of age. Additionally, serum lactate was proposed as a useful surrogate marker of tissue hypoperfusion. However, it is not required to diagnose shock in children. Pediatric mortality from septic shock remains high, even if lactate levels are not elevated; lactate levels > 2 mmol/L (32.0% mortality) versus lactate levels < 2 mmol/L (16.1% mortality).[5]

Management

The Best Practice Statement from the SSC recommends implementing a protocol or "bundle" for the management of children with presumed sepsis.[1] A study evaluating 1,179 pediatric patients across 54 hospitals in New York demonstrated that initiation of a sepsis bundle within one hour of recognition resulted in lower risk-adjusted odds of in-hospital mortality (OR 0.59 [95% CI, 0.38 to 0.93], p=0.02; with a predicted risk difference (RD) of 4% [95% CI, 0.9% to 7.0%]. Each hospital created its own unique sepsis bundle, with all containing three common elements: 1) blood culture collection within one hour, before antibiotics, 2) administration of broad-spectrum antibiotics

Table 1. Definitions used in Pediatric Sepsis. Adapted from Goldstein, et al. WBC = white blood cell count, ARDS = acute respiratory distress syndrome

Condition	
Systemic Inflammatory Response Syndrome (SIRS)	Presence of ≥ 2 of the following: Core temperature ≥38.5°C or < 36°C Increased heart rate for age Tachypnea for age Increased or decreased WBC, or > 10% bands
Sepsis	SIRS in presence of suspected or proven infection.
Severe Sepsis	Sepsis + one of following: cardiovascular dysfunction, ARDS, or ≥ 2 other organ systems dysfunctions
Septic Shock	Sepsis and cardiovascular organ dysfunction.

within one hour of recognition, and 3) administration of a 20 mL/kg fluid bolus.[6] A resuscitation algorithm for children has been developed by the SSC that emphasizes immediately establishing intravenous (IV) or intraosseous (IO) access, obtaining blood cultures, and administering empiric broad-spectrum antibiotics within the first hour of sepsis recognition (See Figure 1).[7]

Given the dynamic nature of sepsis, the initial resuscitation phase is characterized by frequent patient reassessment and careful attention to fluid management to both optimize resuscitation and minimize potential fluid overload. The updated guidelines recommend timely broad-spectrum antibiotics: within one hour for septic shock and within three hours of initial suspicion of sepsis (See Figure 1). It is recommended that isotonic crystalloids be used in 10-20 mL/kg bolus doses until volume resuscitation is attained, or there is clinical evidence of fluid overload. Up to 40-60 mL/kg of fluid resuscitation should occur within the first hour of septic shock or sepsis-associated organ dysfunction, although some pediatric patients with severe shock require much more volume resuscitation. Adequate volume resuscitation is characterized by good perfusion, improved capillary refill time, and strong pulses on examination, not by what the cardiopulmonary monitor demonstrates. Oftentimes, good urine output and improved mental status can be used as reassuring signs of adequate end-organ perfusion.

Starting an epinephrine infusion is prudent if concerns for myocardial dysfunction exist. Epinephrine and/or norepinephrine infusion may be necessary if shock persists after 40-60 mL/kg of fluid resuscitation, or sooner if fluid overload is evident (See Figure 2).

Norepinephrine is the vasoactive medication of choice in children with signs of "warm shock." Epinephrine and norepinephrine can be administered through an IO, or an IV in diluted concentrations, while awaiting placement of central venous access. Lack of central access should not dissuade providers from early administration of inotropes.

Care should also be taken to closely monitor serum electrolytes in children with sepsis or shock. Hypocalcemia and hypoglycemia are frequently seen in sepsis and should be replenished once identified.

Conclusion

Recognizing pediatric sepsis and shock is challenging, but imperative. Establishing IV/IO access, obtaining blood cultures, and starting broad-spectrum antibiotics within the first hour of recognition, along with judicious fluid resuscitation with frequent patient-reassessment is the key to successful management. Developing a sepsis bundle that is designed based upon local resources is essential and will lead to improved outcomes.

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Eruptive Xanthoma

Abstract

A pleasant, 27-year-old white man presented to our clinic for a second opinion about a one-year history of worsening bumps on his skin. He states that he was diagnosed with molluscum contagiosum but is not responding to treatment. He admits to a history of hypertension and type 1 diabetes mellitus but due to financial situation has not been able to afford his medicines. He admits to only taking multivitamins. He denies tobacco and alcohol use. On physical examination, he has too numerous to count multiple yellow grouped umbilicated papules, some coalescing into plaques, scattered on the body. A presumptive diagnosis of eruptive xanthomas was made. A skin biopsy was performed that confirmed the diagnosis. Laboratory evaluation was performed. Pertinent abnormal tests include total cholesterol 444 (0-200 mg/dL0, triglycerides 3176 (0-150 mg/dL), HDL 14 (40-60 mg/dL), glucose 423 (70-105 mg/dL), creatinine 1.30 (0.72-1.25 mg/dL). He was referred to our local free clinic. He now is being treated for his diabetes and hyperlipidemia. The skin lesions started resolving after one month of medications and no cutaneous interventions.

Discussion

Cutaneous manifestations of systemic diseases are paramount for all health care professionals to know. Xanthomas are cutaneous manifestations of hyperlipidemia. They can present as plaques, papules, or nodules that consist of an accumulation of lipids. Xanthomas occur most commonly in the skin and tendons.[1] The pathogenesis of xanthomas is related to the abnormal accumulation of lipid-laden macrophages in the skin; this is due to primary lipid disorders or secondary causes of hyperlipidemia that include metabolic diseases, hepatic diseases, hematologic disorders, and as side effects of drugs.[2] Xanthomas that occur in normolipemic patients, termed normolipemic xanthomas, are much rarer occurrences.

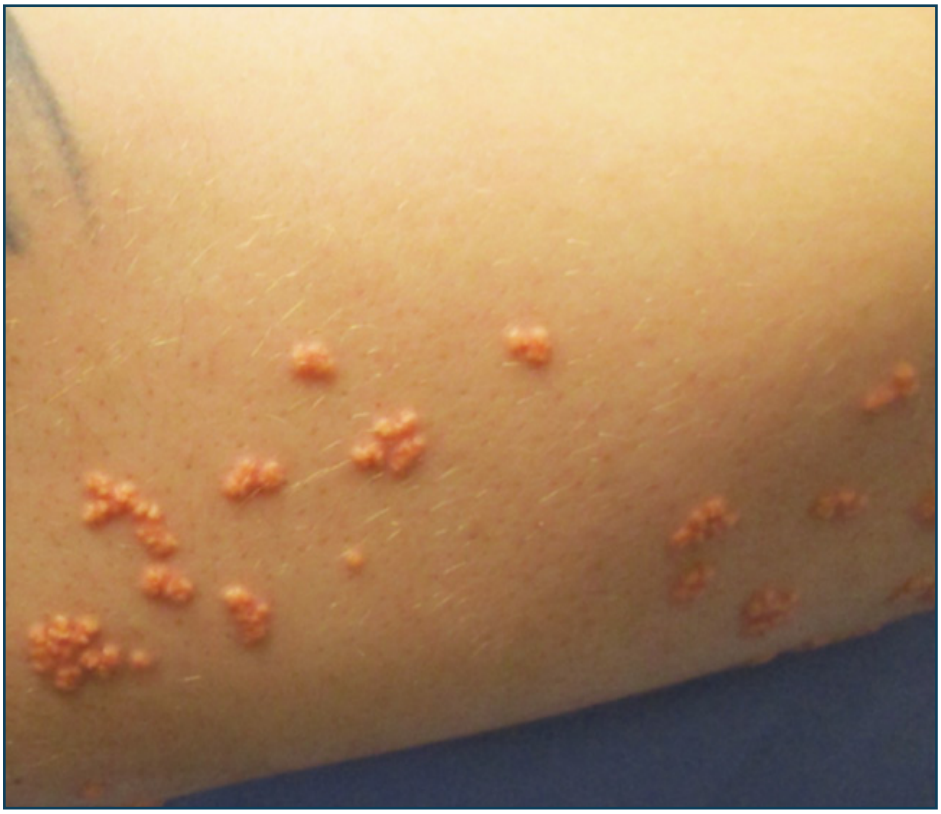

Figure 1: Multiple yellow, grouped umbilicated papules, some coalescing into plaques, scattered on the right upper arm.violaceous periocular rash.

Eruptive xanthomas are discrete, inflammatory-type papules that usually present in clusters around the buttocks, elbows, lower arms, or knees.[2] The primary lipid disorders most often associated with eruptive xanthomas are primary hyperchylomicronemia and familial hypertriglyceridemia.[2] Obesity, cholestasis, uncontrolled diabetes, and medications such as retinoids, estrogen therapy, and protease inhibitors are the most common secondary causes of hyperlipidemia associated with eruptive xanthomas. Importantly, the most common setting in which eruptive xanthomas occur is with uncontrolled diabetes, which was the case for our patient.[3]

On physical examination, eruptive xanthomas appear as dome-shaped, discrete, papules that are initially red, but later become yellow with a surrounding red halo.[2] Notably, eruptive xanthomas display the Koebner phenomenon, in which the lesions can occur secondary to skin trauma.[1] As in our patient, the triglyceride levels in patients with eruptive xanthomas are markedly elevated, frequently being above 1,000 mg/dL. When suspecting eruptive xanthomas, one must also keep in mind the differential diagnoses, which include

generalized granuloma annulare, molluscum contagiosum, sub-epidermal calcified nodules, xanthoma disseminatum, and sarcoidosis.[2] Our patient was diagnosed with multiple molluscum contagiosum but did not respond to treatment. Moreover, there have been many cases of eruptive xanthomas misdiagnosed as molluscum contagiosum reported in the literature.[4,5]

The management of all xanthomas involves treating the underlying hyperlipidemia, as the cutaneous lesions most often resolve once the patient's lipid levels have improved. Although xanthomas are often a more cosmetic concern, it is imperative that the underlying cause be treated as there is increased morbidity and mortality associated with untreated hyperlipidemia.[1] The most common interventions to reduce lipid levels include lifestyle changes such as increased aerobic exercise, reduced smoking, and therapeutic diets along with weight management. Lipid-lowering agents are also frequently administered to help address the underlying hyperlipidemia, with differing agents used to treat different lipid abnormalities. Statins are often immediately initiated in patients who have risk factors for atherosclerotic disease such as hyperlipidemia, although their primary mechanism is to reduce LDL-cholesterol. This is due to numerous studies showing that statins have cardio-protective effects and reduce the risk of major adverse cardiovascular events.[6-8] However, in eruptive xanthomas, where the triglyceride and chylomicrons levels are often extremely high, fibrates work more directly than statins to reduce these parameters. Thus, fibrates are often used as adjuvant therapy with statins, especially in patients with eruptive xanthomas. Other agents used include bile acid resins, niacin, omega-3 fatty acids, and PCSK9 inhibitors. The latter of these have recently been FDA approved for the treatment of dyslipidemias in patients who have been refractory to standard medical therapy. Finally, the definitive management of eruptive xanthomas involves surgical excision, especially if they are refractory to medical therapy or cause severe discomfort. Newer modalities of removal also include ablative laser therapy and cryotherapy.

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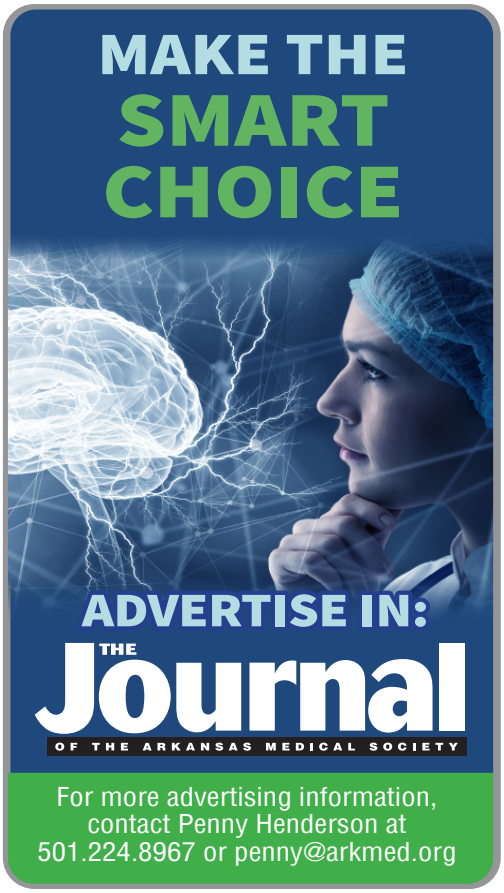

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