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Infections after Natural Disasters

Pancreatitis

Sexually Transmitted Infections Part 2: Discharge Syndromes and Pelvic Inflammatory Disease

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BEXSERO
Meningococcal Group B Vaccine

GOING HALFWAY

The person depicted here is a model used for illustrative purposes only.

It takes 2 doses to complete the BEXSERO vaccination series[1]

According to 2018 CDC survey data, **only 17.2% of 17-year-olds had received at least 1 dose of a meningococcal serogroup B (MenB) vaccine.**[2] That means you could have patients who started the series and haven't come back for their second dose. And since there's no telling if a patient will return to your office to finish the series on their own, it's important that you remind them.

CDC=Centers for Disease Control and Prevention.

Indication for BEXSERO

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals aged 10 through 25 years.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic reaction following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)

DOESN'T CUT IT

Consider scheduling the second dose during the holiday break

Remember: BEXSERO offers the fastest MenB vaccination series—allowing you to complete vaccination with 2 doses in as fast as 1 month.[1,3]

Vaccination may not protect all recipients.

Learn more about creating a MenB vaccination protocol in your practice

Visit ***ScheduleTheSeries.com***

Important Safety Information for BEXSERO (cont'd)

- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Some individuals with altered immunocompetence may have reduced immune responses to BEXSERO
- Individuals with certain complement deficiencies and individuals receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *Neisseria meningitidis* serogroup B even if they develop antibodies following vaccination with BEXSERO
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see Brief Summary of Prescribing Information for BEXSERO following this ad.

References: 1. Prescribing Information for BEXSERO. **2.** Centers for Disease Control and Prevention. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years—United States, 2018. *MMWR*. 2019;68(33):718-723. **3.** Prescribing Information for Trumenba.

BRIEF SUMMARY

BEXSERO (Meningococcal Group B Vaccine)
suspension, for intramuscular injection

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals aged 10 through 25 years.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO *[see Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.4 Limitation of Vaccine Effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information*].

5.5 Altered Immunocompetence

Some Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

Complement Deficiency

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis* serogroup B even if they develop antibodies following vaccination with BEXSERO *[see Clinical Pharmacology (12.1) of full prescribing information]*.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In 4 clinical trials, 3,058 individuals aged 10 through 25 years received at least one dose of BEXSERO, 1,436 participants received only BEXSERO, 2,089 received only placebo or a control vaccine, and 1,622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in U.S. and Poland, 120 participants aged 10 through 25 years received at least 1 dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49%, and 60% were white, 34% were Hispanic, 4% were black, <1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) aged 11 through 17 years received at least 1 dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (U.K.), 974 university students aged 18 through 24 years received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of MENVEO followed by 1 dose of placebo containing aluminum hydroxide (n=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (n=947). Across groups, median age was 20 years, males comprised 46%, and 88% were white, 5% were Asian, 2% were black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants aged 11 through 17 years received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were white, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, U.S./Poland, Canada/Australia, and in a subset of participants in the U.K. study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the U.S./Poland study, reports of unsolicited adverse events were collected up to 1 month after the second vaccination.

Reports of all serious adverse events, medically attended adverse events, and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), U.K. (12 months), U.S./Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants aged 10 through 25 years following each dose of BEXSERO administered 2 months apart or control in the U.S./Polish study[1] are presented in Table 1.

Table 1: Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Solicited Local and Systemic Adverse Reactions within 7 Days after BEXSERO or Control, by Dose

		Dose 1		Dose 2[b]	
		BEXSERO	Placebo (Saline)	BEXSERO	MENVEO
Solicited Reaction[a]		**n = 110-114**	**n = 94-96**	**n = 107-109**	**n = 90-92**
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	>50-100 mm	1	1	2	4
	>100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema and induration: Any (≥1 mm). Pain and systemic reactions: Mild (transient with no limitation in normal daily activity); Moderate (some limitation in normal daily activity); Severe (unable to perform normal daily activity).

[b] Administered 2 months after Dose 1.

(continued on next page)

Solicited adverse reaction rates were similar among participants aged 11 through 24 years who received BEXSERO in the other 3 clinical studies,[2,3,4] except for severe myalgia which was reported by 3% to 7% of subjects. Severe pain was reported by 8% of university students in the U.K.[3]

Non-serious Adverse Reactions

In the 3 controlled studies[1,2,3] (BEXSERO n=2,221, control n=2,204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) participants receiving BEXSERO and 197 (9%) control recipients. Unsolicited adverse reactions that were reported among at least 2% of participants and were more frequently reported in participants receiving BEXSERO than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants aged 10 through 25 years who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO n=2,716, control n=2,078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) participants receiving BEXSERO and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at 2 universities in the U.S., BEXSERO was administered as a 2-dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals aged 16 through 65 years who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one reaction considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BEXSERO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site, and injection site nodule which may persist for more than 1 month).

Immune System Disorders

Allergic reactions (including anaphylactic reactions), rash, eye swelling.

Nervous System Disorders

Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of BEXSERO in pregnant women in the U.S. Available human data on BEXSERO administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study was performed in female rabbits administered BEXSERO prior to mating and during gestation. The dose was 0.5 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to BEXSERO (*see Data*).

Data

Animal Data: In a developmental toxicity study, female rabbits were administered BEXSERO by intramuscular injection on Days 29, 15, and 1 prior to mating and on Gestation Days 7 and 20. The total dose was 0.5 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to Postnatal Day 29 were observed. There were no fetal malformations or variations observed.

8.2 Lactation

Risk Summary

It is not known whether the vaccine components of BEXSERO are excreted in human milk. Available data are not sufficient to assess the effects of BEXSERO on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BEXSERO and any potential adverse effects on the breastfed child from BEXSERO or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years.

15 REFERENCES

1. NCT01272180 (V102_03).
2. NCT00661713 (V72P10).
3. NCT01214850 (V72_29).
4. NCT01423084 (V72_41).

17 PATIENT COUNSELING INFORMATION

Give the patient, parent, or guardian the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Inform patients, parents, or guardians about:

- The importance of completing the immunization series.
- Reporting any adverse reactions to their healthcare provider.

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Infections after Natural Disasters

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PRACTICE GAPS

- Physicians should be aware of infections that can appear during various types of natural disasters like hurricanes, earthquakes, and flooding, including water and mosquito borne pathogens like Zika virus and West Nile virus.
- Physicians should be aware of infection prevention and mitigation strategies for natural disasters.

OBJECTIVES *After reading this article, readers should be able to:*

1. Recognize types of infections that may occur in various stages after a natural disaster.
2. Recognize the causes of increased risk of infections after a natural disaster.
3. Participate in predisaster planning.

ABSTRACT

Natural disasters, particularly flooding, are associated with many environmental changes, and the chances of infections after a disaster increase. Dead bodies are not associated with increased infections, but many other factors contribute to the increase in infections and possible outbreaks. This article discusses the factors associated with increased risk of infections and the types of infections that may occur after a natural disaster. This article also presents a brief discussion of infection prevention and mitigation after a natural disaster.

One often-used definition of disaster is "a vast ecological breakdown in the relation between humans and their environment, a serious or sudden event on such a scale that the stricken community needs extraordinary efforts to cope with it, often with outside help or international aid." (1) Disasters can strike anywhere in the world and can be natural or manmade. In this article, we focus on natural disasters, specifically, flooding. Authorities all over the world prepare responses to disasters, and disaster preparedness has improved over the years. Responding to disasters is expensive and in large part depends on the resources available to countries and affected regions.

Whereas international relief organizations attempt to assist the underresourced parts of the world postdisaster, planning done before a disaster is critical. High-

AUTHOR DISCLOSURE Dr Rathore has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

resourced countries can plan better for disasters; nevertheless, major disasters can still challenge the limits of disaster planning. Even in high-resourced countries, regions with poor public health infrastructure are vulnerable. Two vivid examples are how Hurricane Maria affected Puerto Rico and how Hurricane Katrina affected the Lower Ninth Ward of New Orleans. Unpredictable and sudden disasters such as earthquakes and avalanches are more difficult to manage and respond to effectively. Slow-moving and predictable disasters such as hurricanes and typhoons can allow more effective responses. Nevertheless, postdisaster responses and attempts at infection control after any type of natural disaster, whether unexpected or predictable, can be a huge challenge. Herein we provide a framework to help readers better understand what to expect regarding postdisaster infections.

The recent hurricanes that affected parts of the United States and the floods that followed have increased interest in better understanding infections that may be associated with these natural disasters (eg, see https://www-m.cnn.com/2018/07/03/health/sutter-leptospirosis-outbreak-puerto-rico-invs/index.html)

While the public may not be as aware of postdisaster infections, emergency response planners are concerned about major infectious disease outbreaks following a natural disaster. Although there are reports in the medical literature of serious outbreaks of infectious diseases after natural disasters, outbreaks are a rare occurrence. Data on infectious diseases associated with natural disasters are limited and are mostly from studies of adult populations. Hurricane Maria, which devastated Puerto Rico, exposed the challenges of collecting accurate data for infection outbreaks after natural disasters.

CLASSIFICATIONS AND DEFINITIONS

Types of Disasters

Disaster management experts stratify natural disasters into several categories that help plan for postdisaster management. One classification divides natural disasters broadly into 3 general types (Table 1). This is merely a stratification of convenience and is not meant to be exclusive. Any disaster in one category can have elements that are present in another. For example, flooding, typically associated with hurricanes and heavy rainfall, can follow landslides. Similarly, earthquakes can cause avalanches and tsunamis, which can, in turn, cause flooding.

Postdisaster Phases

Disasters are classified into various stages for the purpose of planning. Disaster management experts use 4 stages: mitigation, preparedness, response, and recovery. (2) Disaster response has been classified into 3 stages: relief, recovery, and rebuilding. For understanding postdisaster infections, 3 phases should be considered: impact, postimpact, and recovery. (3) These 3 phases can be helpful for postdisaster management and planning for infectious diseases (Table 2). This stratification provides a tool for health-care professionals to better prepare for different types of infections. This is not, however, a strict linear model. There can be significant overlap in the various phases. Although certain infections should be considered more likely in one phase or another, certainly no postdisaster infection is limited to any single phase.

Outbreak versus Epidemic

Any natural disaster causes a major disruption of the normal environmental ecology of the affected region. With floods, this disruption may cause increased risk of infections that are usually endemic to the region, resulting in higher-than-usual infections in the population, which may or may not result in outbreaks or epidemics. Although the terms *outbreak* and *epidemic* are used interchangeably, they are slightly different. An outbreak may be defined as an increase in the number of reported infections in an area over the typical incidence rate for that type of infection. Outbreaks tend to be more localized. As an example, there have been recent reports of measles outbreaks noted in several communities in the United States. Epidemics, on the other hand, may be defined as the occurrence of a new or unusual infection affecting a large population spread over an entire geographic region. An example of an epidemic would be the spread of cholera throughout Haiti and the Dominican Republic following the catastrophic earthquake in 2010. The underresourced parts of the world are particularly vulnerable to infectious outbreaks and epidemics that may be caused by natural disasters. Even high-resourced countries are not immune to outbreaks. In high-resourced countries it is areas of poverty, social inequality, and weak infrastructure, similar to in

Table 1. Classification of Natural Disasters

Hydrometeorological disasters	Most common	Floods from rains, hurricanes, cyclones, typhoons, tsunamis
Geophysical disasters	Second most common	Earthquakes (land or underwater), volcanic eruptions
Geometeorological disasters		Landslides (mud or rock), avalanches

Table 2. Phases of Postdisaster Infections

Phase 1	Impact phase (immediate, acute)	0–4 d	Infections associated with injuries and soft tissue infections
Phase 2	Post–impact phase (early)	4 d–4 wk	First wave of infectious diseases (airborne, foodborne, vectorborne)
Phase 3	Recovery phase (late)	After 4 wk	Infections with long incubation periods and latent infections

underresourced countries, that are most affected by infectious outbreaks.

TYPES OF INFECTIOUS DISEASES AFTER NATURAL DISASTERS

Understanding what types of infectious diseases are more likely to occur in which postdisaster phase assists in planning postdisaster management. In this article, we focus on hydrometeorological natural disasters and use the phase stratification shown in Table 2. We focus on the risk of types of infections after flooding, regardless of the cause of the flood. According to the World Health Organization, floods are responsible for 40% of natural disasters and are more likely to be associated with vectorborne and waterborne infections. (4) Although infections are different (with some overlap) in the 3 postdisaster phases, the post–natural disaster infectious diseases can be divided into several distinct groups (Table 3).

MYTH THAT CORPSES CAN CAUSE OUTBREAKS AFTER DISASTER

There often are concerns about infectious disease outbreaks due to exposed, unprotected dead bodies that may be present after a natural disaster. There is no evidence that corpses are associated with increased risk of infectious outbreaks after a natural disaster. (5) In fact, postdisaster infections are more likely to be spread among the survivors than spread from the dead to survivors.

FACTORS ASSOCIATED WITH INCREASED RISK OF INFECTIONS

Several factors contribute toward an increased risk of infectious outbreaks after a natural disaster (Table 4). Population displacement and overcrowding in shelters or camps are the most important factors that contribute to increased risk of postdisaster infections. Some of the other factors that contribute to post–natural disaster infectious outbreaks are the disruption of the supply of safe drinking water and safe food plus poor hygiene in the displaced population. However, the breakdown of the all-important public health system can be a significant factor in the uncontrolled spread of infectious diseases. Lack of trained public health professionals who can respond to an infectious outbreak and lack of resources, including vaccines and antimicrobials for chemoprophylaxis, can be significant detriments. Decreased investment in and scaling back of public health systems are significant contributors to the risk of a public health system breakdown. In addition, this weakness in the public health infrastructure also results in the inability to scale up the public health response in the case of a public health crisis of any kind. This is especially true for postdisaster infections due to the lack of resources and trained and experienced public health personnel who understand how to respond to an outbreak or an epidemic. For example, the lack of a robust vector control program before flooding can only make the risk of vectorborne disease spreading after flooding worse.

The risk of infectious outbreaks is more from survivors, especially the susceptible and vulnerable survivors who are nonimmune and susceptible to particular infections. One other factor to consider is that infected and contagious patients may have an interruption of their ongoing treatments. Although diagnosed before the natural disaster, potentially contagious diseases, such as tuberculosis, can suddenly become a potential problem after a disaster. The youngest and the elderly affected by natural disasters are at increased risk for acquiring and spreading an infectious disease. One important factor that increases the risk of postdisaster infectious outbreaks is the low level of immunizations against vaccine-preventable diseases before the disaster. A population that is susceptible to, say, measles is much more likely to experience an outbreak of measles in the affected population. Measles outbreaks occur in populations that have low immunization rates even under normal circumstances. Disasters exacerbate susceptibility to infections.

The epidemiological triad of host, environment, and infectious agents is a well-accepted concept in the spread of infectious diseases. The perfect storm unsettling this epidemiological triad consists of population displacement (hosts), environmental disruption by the natural disaster, and opportunity enhancement for pathogens to cause infections after a natural disaster. The host is the population that is

Table 3. Classification of Postdisaster Infections

Waterborne diseases
Foodborne diseases
Respiratory infections
Dermatologic infections
Diseases associated with overcrowding
Vectorborne diseases
Diseases related to change in the environment

affected by the natural disaster, especially those vulnerable and susceptible who are displaced and housed in close quarters in shelters or camps. The environment can have major ecological disruption, unsafe water and food, and soil disruption. The infectious agents are usually organisms endemic to the region, but they can also be nonendemic. Natural disasters are an ideal scenario for easy transmission of potentially contagious diseases.

The lack of robust data about the epidemiology and nature of infections after a natural disaster that would inform us about the presence and spread of infectious diseases after natural disasters poses another challenge. The reported data that exist are mostly descriptive. However, a better understanding of infectious disease outbreaks after a natural disaster would allow for better planning and preparation for post–natural disaster infectious outbreaks and epidemics.

Outbreaks are often not related directly to natural disasters themselves, but rather outbreaks occur secondary to the environmental changes, population displacement, and disruption of services after a natural disaster. It is a myth that infectious outbreaks are an inevitable result of natural disasters. The most common reason is population displacement that often occurs after natural disasters and is often the primary driver of spread of infectious diseases. The displaced population often concentrates in shelters or camps. This increased population density, often in the enclosed environment of a shelter, results in close proximity of people, which results in increased opportunity for transmission of respiratory infection, such as the spread of influenza. This concentrated population, along with disruption of the safe water supply and poor sanitation, is also a perfect setup for the spread of waterborne or foodborne illnesses, such as norovirus infections.

Table 4. Factors that Increase the Risk of Infections after a Natural Disaster

Increased population density in shelters
Poor sanitation
Unsafe water supply
Unsafe food supply
Vulnerable populations (children and elderly)
Low immunization rates
Poor public health infrastructure

INFECTIONS IN THE POSTDISASTER PHASES

Diarrhea and acute respiratory infections are the most common causes of death after a natural disaster (3). Measles and malaria are among the infections (in endemic regions) that are also associated with high mortality. (6) Children 5 years and younger are most likely to be affected by acute respiratory infections. (7)

Listed in Table 5 are some of the factors that determine the types of infections that may occur after a disaster. Table 6 lists various infections of concern after a natural disaster. This is not a comprehensive list. In the appropriate circumstances, almost any infection or infectious outbreak can occur postdisaster.

Impact Phase

Other than an unusual postdisaster outbreak or epidemic scenario, the most common immediate postdisaster concerns are injuries such as fractures, crush trauma, lacerations, burns, near drownings and drownings, missile injuries, blunt injuries, animal and snake bites, and electrocutions from fallen power lines that may result in minor to significant morbidity and even death.

There are usually no infectious outbreaks in the impact phase of natural disasters. In this phase (sometimes referred to as the early acute phase), infected wounds and snake or animal bites are more likely to be seen. (8)(9) Infections in the impact phase, if they occur, are usually respiratory, gastrointestinal, or dermatologic. The organisms causing these infections in the impact phase are usually the ones that occur in that population under normal conditions. In the impact phase, because of the close proximity between people in the high-density population of a shelter or of camps, infections are seen more frequently in a shorter period. Some other infections not commonly seen or seen seasonally, such as influenza, norovirus, and methicillin-resistant *Staphylococcus aureus*, may spread quickly in the displaced population. In parts of the world with low rates of immunization, tetanus can occur after injuries, and measles can rapidly spread in the impact phase due to its high R_o ratio, or ability to spread to other susceptible hosts, often referred to as contagiousness. (10) Appropriate wound management should include use of tetanus toxoid (and/or tetanus

immunoglobulin) for the prevention of tetanus. The Centers for Disease Control and Prevention (CDC) website provides more details for tetanus prophylaxis (https://www.cdc.gov/tetanus/clinicians.html). If prophylaxis is not done, tetanus may appear in the postimpact phase.

Postimpact Phase

It is in the postimpact phase that infectious outbreaks are most likely to be seen. The infections alluded to previously herein in the impact phase are also more likely to occur in the postimpact phase even if the spread started in the impact phase.

In the postimpact phase, waterborne and foodborne diseases such as rotavirus, norovirus, dysentery, cholera, typhoid and paratyphoid, cryptosporidium, giardia, and hepatitis A and E are the ones more likely to be seen. (10)(11)(12)(13)(14)(15) Leptospirosis is caused by close proximity with rodents (16)(17). Climate also plays an important role in the type of infection outbreaks. For example, a warm climate favors enterovirus infection and transmission, and winter favors rotavirus infection and transmission. Norovirus diarrhea can spread quickly in individuals who previously have not had norovirus infection, and rotavirus diarrhea can quickly spread in unimmunized children. In a temperate climate, such as in the United States, winter is associated with seasonal influenza outbreaks and transmission. The respiratory diseases seen in the postimpact phase include the usual viral infections: rhinovirus, respiratory syncytial virus, and adenovirus. (18) Bacterial respiratory infections caused by *Streptococcus pneumoniae* and *Bordetella pertussis* are more likely in unimmunized children.

An undiagnosed case of contagious tuberculosis or a known case of tuberculosis not being treated because of unavailability of medications after a disaster and disruption of the public health system can serve as an index case and spread to others during the postimpact (and possibly impact) phase but may not come to light until the recovery phase. However, if a contagious case is identified and quarantined and contact investigation is conducted immediately, the spread of tuberculosis infection or disease could be prevented. Preventing the spread of tuberculosis could be a huge challenge in the postdisaster chaos. Infections caused by *Legionella* and *Mycoplasma* are also high on the list of respiratory infections that can potentially spread very quickly and cause an outbreak.

Aspiration pneumonia may be seen after flooding secondary to aspiration of flood waters. A particular type of pneumonia caused by seawater due to the aspiration of saltwater that was soil contaminated has been described. This condition was seen after a tsunami in Southeast Asia and was dubbed "tsunami lung." (19) Tsunami lung is a polymicrobial infection often reflecting the endemic regional soil organisms. Tsunami lung can be seen in both the postimpact and recovery phases of natural disasters.

Recovery Phase

It is in the recovery phase that infections with a longer incubation period, such as leishmaniasis and leptospirosis, are likely to appear. This is also the phase to witness vectorborne infections. (7) When flooding occurs, it will initially wash away the usual habitats of mosquito vectors that spread malaria, dengue virus, Zika virus, West Nile virus, Western and St. Louis encephalitis, and yellow fever. However, as waters recede, new habitats are created that allow the mosquitoes to thrive, especially in the absence of a good mosquito control program because of the breakdown of the public health infrastructure.

Wound infections can be seen in any of the phases and are often polymicrobial. (20) Organisms may include *Staphylococcus* (including methicillin-resistant *Staphylococcus aureus*) or *Streptococcus* that exist on the skin (21). However, infectious organisms likely to be seen include enteric organisms (*Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*) or hydrophilic organisms (*Aeromonas, Plesiomonas*). Depending on the geographic location of the disaster, organisms that are endemic to the region may cause wound

Table 5. Risk Factors for Disease Transmission

1. Environmental factors
a. Climate: cold, more likely airborne infections versus warm, more likely waterborne infections
b. Season: winter, more likely influenza, respiratory syncytial virus, and other respiratory viruses versus summer, enteroviruses versus fall, influenza and enteroviruses
2. Endemic pathogens
3. Population characteristics
4. Public health infrastructure: sanitation, nutrition, primary care, disaster preparedness, surveillance, equipment, medication stockpile, transportation, medical infrastructure
5. Type of disaster

Table 6. Postdisaster Infections

Waterborne diseases	Cholera
Foodborne diseases	Leptospirosis Hepatitis A Hepatitis E Bacillary dysentery Typhoid fever
Respiratory infections	Respiratory syncytial virus Influenza Measles Meningitis Pneumonia Tuberculosis
Dermatologic infections	*Staphylococcus aureus* (including methicillin-resistant *S aureus*) *Vibrio vulnificus* *Vibrio parahemolyticus* Nontuberculous mycobacteria Melioidosis *Aeromonas* *Plesiomonas*
Diseases associated with overcrowding	Dermatologic and respiratory
Vectorborne diseases	Malaria Dengue virus West Nile virus Yellow fever Zika virus Chikungunya Japanese encephalitis
Diseases related to change in the environment	Coccidioidomycosis

Detail of individual diseases is available in: American Academy of Pediatrics. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL; American Academy of Pediatrics; 2018.

infections. After Hurricane Katrina in New Orleans, wound infections were seen with *Vibrio vulnificus* and *Vibrio parahemolyticus*. (22) Both coccidioidomycosis in California (23) and giardia in Montana (24) have been reported as examples of endemic organisms causing outbreaks after natural disasters. Melioidosis was seen after flooding in regions where *Burkholderia pseudomallei* is endemic. (25)(26)

Although mold infections are not very common, mold-related infections were seen after Hurricane Katrina in the recovery phase (27). As residents return to their homes and start recovery efforts, mold can appear in the homes and can potentially go unnoticed. Ensuring that dwellings that were flooded are free of mold should be part of the recovery effort to prevent serious mold-associated infections.

It is also possible that relief workers arriving to the disaster area from different parts of the world may introduce a non-endemic infection after a natural disaster. Such workers can bring infections endemic in their countries of origin. This was the reason for the cholera outbreak in the local Haitian population after the earthquake in Haiti. Cholera was introduced by the Nepalese military brought in by the United Nations. (28) It is very conceivable that relief workers may be incubating infections that can then spread to the susceptible population in the disaster area. Measles can be carried by relief workers and can spread easily in shelters and camps. Combating the spread of measles depends largely on the immunization status of the population affected by the disaster. It is also possible that a vectorborne infection, such as Dengue or Zika virus, can be transmitted if the vector exists in the disaster area. This is especially a concern after flooding as waters recede and pockets of water collection can become ideal habitats for mosquito vectors. With the decrease in vector control funding in many American jurisdictions where the mosquito vectors are endemic after disasters, there can be a resurgence of mosquitos. Because the vector control infrastructure has been dismantled or severely scaled back, it may be a huge challenge to provide enough vector control resources.

INFECTION PREVENTION AND MITIGATION STRATEGIES

A detailed discussion of infection prevention and mitigation strategies is beyond the scope of this article and is usually not the responsibility of pediatricians. However, pediatricians must be well versed in infection prevention and control (IPC) concepts and requirements. (29)(30) In general, IPC strategies after a natural disaster are similar to those under normal circumstances. However, adequate preparation for IPC becomes the responsibility of authorities managing postdisaster efforts. IPC must be planned before a disaster occurrence. There are special considerations for control and mitigation of infections after a disaster because some infections seen after a natural disaster are not the usual infections seen in the absence of a disaster. (31)(32) The CDC provides guidance for IPC and infection mitigation. (33)(34) Evacuation centers should be prepared to prevent the spread of infections, especially respiratory and diarrheal illnesses. Hand hygiene remains the key element, but use of personal protective equipment and quarantine and cohorting of sick individuals are also important elements of postdisaster infection prevention and mitigation strategies. Provision of safe drinking water and food supplies is critical, as is availability of water for personal hygiene. Masks and gloves should be available for health-care providers and infected evacuees. Pediatricians may be called on to assist in an evacuation center. In addition to routine vaccines, displaced children in crowded, high-

Table 7. Essential Elements of Postdisaster Infection Prevention and Mitigation Planning

1. Preparation for infectious outbreak in predisaster planning
2. Identification of risk factors for endemic infectious diseases
3. Presence of surveillance and early warning systems
4. System to identify introduction of nonendemic infections
5. Staging of safe drinking water and food supplies
6. Staging of medical supplies, including personal protective equipment
7. Availability of medications, including antimicrobials and vaccines
8. Deployment of volunteer health corps
9. Vector control
10. Crisis communication (rumor prevention)

density evacuation centers may benefit from measles-mumps-rubella and varicella vaccines depending on age and, depending on the time of the disaster, influenza vaccine. (34)

Health-care facilities must also be prepared to deal with the postdisaster infection prevention and mitigation response. Health-care facilities must plan adequately for the possibility of working with low levels of supplies and personnel but also for access to outside help. In most jurisdictions, health-care facilities work with their city, county, and state emergency operation leadership. Children often have additional special needs, and pediatricians should serve in an advisory capacity to the emergency operation group in their jurisdiction. The American Academy of Pediatrics (AAP) has advocated for appropriate postdisaster resources for children. The AAP, through its Disaster Preparedness Advisory Council (DPAC), has very effectively advocated for children at the national level. The DPAC also provides a tremendous amount of guidance through its policies and other documents (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/Disaster-Preparedness-Advisory-Council.aspx). However, it is essential that pediatricians, through their AAP chapters and local pediatric societies, work hand-in-hand with the emergency operation groups to make sure that the needs of children are met. (34) The predisaster emergency plan should include a specific plan for children, especially for children with special health-care needs and those who are technology dependent. Pediatricians should have a disaster preparedness plan for their offices.

Pediatricians should also sign up for volunteer health corps and receive appropriate training and credentialing to be able to work after a disaster hits their area.

Emergency operation groups and public health authorities should plan for several important postdisaster elements that can lead to increased infections, outbreaks, and epidemics. These plans should include not only how to prevent infectious disease outbreaks postdisaster but also how to address when infectious disease outbreaks do occur. Table 7 lists some of the important elements of postdisaster infection prevention and mitigation essentials.

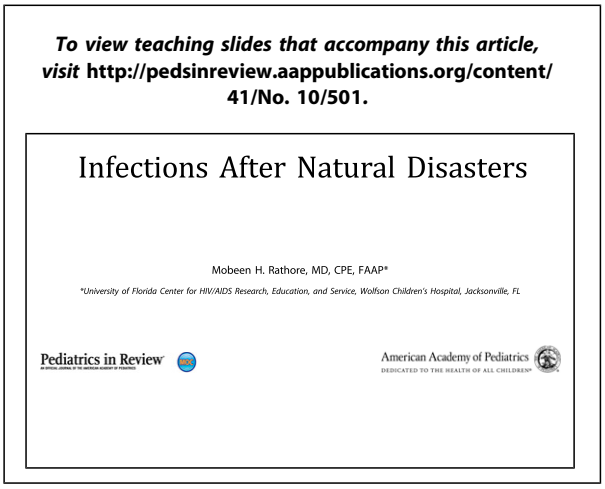
SUMMARY

Although infectious outbreaks are not inevitable after a natural disaster, the risk of infections is elevated. Population displacement and housing people in shelters is one of the major risk factors for infectious outbreaks. Underlying protection against vaccine-preventable diseases is important in preventing outbreaks. Infections after a natural disaster may be due to commonly seen infections. However, unusual and rare infections can also cause infections after a natural disaster. Types of infection vary depending on the postdisaster stage. Understanding which infections are of concern after a natural disaster and being prepared to respond to these infections is key. A strong public health infrastructure is also key.

SUGGESTED QUALITY IMPROVEMENT PROJECTS

- Decrease the rates of infections following disasters.
- Improve the number of measures implemented to decrease infections.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/41/No. 10/501.**



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PIR QUIZ

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1. A group of pediatricians arrived in an underresourced country as part of an emergency operation group after the country experienced a severe hurricane 3 days ago. The area is experiencing severe flooding as a result of the hurricane. Various areas of the country have been disconnected due to blocked roads by fallen trees and flooding. A large number of the population has been displaced due to property loss. Which of the following is the most important factor contributing to the potential increased risk of infection in this setting?

   A. Exposed corpses.
   B. Lack of available antimicrobial agents.
   C. Lack of available vaccines.
   D. Lack of safe food.
   E. Overcrowding in shelters.

2. Two weeks after a severe hurricane devastated a remote underresourced island, a measles outbreak became evident among the island's inhabitants. Which of the following is the most likely contributing factor to the development of this outbreak?

   A. A highly susceptible population.
   B. Genetic mutation of measles virus after the disaster.
   C. Importation of measles virus by relief workers.
   D. Lack of available measles vaccine.
   E. Malnutrition.

3. You are among a group of pediatricians caring for children at an evacuation center 2 days after a severe tornado ravaged a rural area. Which of the following infections is most likely to be affecting the children at this time?

   A. Giardia.
   B. Hepatitis A.
   C. Influenza.
   D. Norovirus.
   E. Wound infection.

4. A group of pediatricians is part of an emergency operation group planning to travel to an underresourced country 2 weeks after a hurricane resulted in severe flooding of the country and mass displacement of the population. In preparation for the visit, which of the following infectious outbreaks would be expected to be most prevalent in the population at this time?

   A. Dengue virus.
   B. Leishmaniasis.
   C. Malaria.
   D. Norovirus.
   E. Respiratory syncytial virus.

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5. You are among a group of pediatricians traveling to an underresourced tropical country in the Caribbean as part of an ongoing recovery effort. The country experienced severe flooding after a hurricane occurred 6 weeks ago. Which of the following types of infections is most likely to be prevalent at this time?

   A. Animal bite infection.
   B. Aspiration pneumonia.
   C. Foodborne infection.
   D. Puncture wound infection.
   E. Vectorborne infection.

Pancreatitis

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EDUCATION GAPS

1. Fluid management in acute pancreatitis is evolving to include lactated Ringer solution, although more pediatric research is needed.
2. Early enteral nutrition within 24 hours is recommended to avoid prolonged nil per os status and associated morbidity.
3. Prophylactic antibiotics are not recommended.

OBJECTIVES

1. Know the classification of pediatric pancreatitis.
2. Understand the etiology, risk factors, clinical manifestations, approach to diagnosis, and treatment of pancreatitis in children.
3. Recognize current consensus guidelines on early enteral nutrition and aggressive fluid management.
4. Know the complications of pancreatitis in children and their appropriate diagnostic and therapeutic strategies.

INTRODUCTION

Pancreatitis is an inflammatory process of the pancreas presenting as a spectrum of clinical disease. Acute pancreatitis (AP) is a reversible process, but it may progress to acute recurrent pancreatitis (ARP). This increases the risk of developing chronic pancreatitis (CP), which carries higher morbidity due to irreversible pancreatic duct strictures, exocrine pancreatic insufficiency, insulin-dependent diabetes mellitus, and chronic pain. Pancreatitis is occurring at an increasing rate in children, which is troubling given the paucity of research in pediatric patients. Historically, management recommendations for pediatric pancreatitis have evolved based on consensus conferences and research in the adult population. In 2018, consensus guidelines for the management of AP were published for both pediatrics (1)(2)(3) and adult medicine. (4)

CLASSIFICATION OF PEDIATRIC PANCREATITIS

Per the INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE), the 3 categories of pancreatitis are AP, ARP, and CP.

AP in pediatric patients requires at least 2 of the following 3 criteria: 1) abdominal pain suggestive of AP, such as acute onset and epigastric in origin; 2)

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ABBREVIATIONS

AIP	autoimmune pancreatitis
AP	acute pancreatitis
ARP	acute recurrent pancreatitis
CP	chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound ultrasonography
IL	interleukin
LR	lactated Ringer solution
MRCP	magnetic resonance cholangiopancreatography
SIRS	systemic inflammatory response syndrome
TPN	total parenteral nutrition
TUS	transabdominal ultrasonography

serum amylase and/or lipase levels at least 3 times the upper limit of normal; and 3) imaging findings consistent with AP. (5) ARP is defined by at least 2 acute attacks within a year, with interval resolution of pain or normalization of serum pancreatic enzyme levels, or by more than 3 lifetime episodes without evidence of CP. (5)(6) CP requires the presence of exocrine or endocrine insufficiency and histologic and morphologic changes that are irreversible, including fibrosis, islet cell loss, inflammatory cell infiltrates, and intraductal calculi. (5)

AP IN PEDIATRICS

Epidemiology

The incidence of pediatric AP has increased in the past 2 decades, (7) ranging from 0.78 to 13.2 pediatric cases per 100,000 annually in the United Kingdom (8) and the United States, (9) respectively. This increase in incidence is multifactorial, having been linked to heightened awareness, appropriate biochemical testing, increasing multisystem disorders, and the rising prevalence of obesity. (10)(11)

Pathophysiology

The damage associated with pancreatitis occurs after inflammatory cytokine-mediated induction of systemic inflammatory response syndrome (SIRS). (12) Specifically, the initial trigger results in excessive intracellular calcium signals in a few pancreatic acinar cells (Fig 1). (13) This intracellular hypercalcemia prematurely activates intra-acinar pancreatic trypsinogen to trypsin, which then activates other digestive proenzymes and together mediates acinar cell injury via autodigestion. (14) This process is exacerbated by inflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1β, IL-6, and IL-8. Histamine, kallikrein, and bradykinin also contribute to the progression and severity of illness by liberating additional proteases and amplifying the SIRS cycle that causes damage to acinar cells. Oxygen free radicals are thought to be involved in the direct attack of unsaturated phospholipids of the cell membrane, leading to accumulation of lipid degradation products (eg, malonaldehyde and 4-hydroxynonenol) and resulting in increased membrane permeability, protease intracellular leakage, and Ca^{2+} influx. (15)

Protective mechanisms such as autodegradation of trypsin and inhibition of trypsin by pancreatic secretory trypsin inhibitor, alpha-1 antitrypsin, and α2-macroglobulin can negate the initial triggering events. Other defense mechanisms, such as the compensatory anti-inflammatory response syndrome, can offset SIRS via the production of anti-inflammatory cytokines, including IL-4, IL-10, and IL-1ra. (14)(16) However, when the balance shifts toward SIRS, pancreatic necrosis and/or multiple organ failure ensues.

Etiology

The causes of AP in children can be broadly categorized into biliary disorders, systemic conditions, infections, trauma, medications, structural abnormalities, metabolic diseases, genetic mutations, autoimmune disorders, and idiopathic etiologies (Table 1). Furthermore, any of these conditions could lead to ARP or CP.

BILIARY DISORDERS. Gallstones, microlithiasis, sludge, and pancreaticobiliary anomalies are common etiologies of pancreatitis in the pediatric population, accounting for 3% to 30% of cases. (19) In particular, pancreatitis should be suspected if the presentation includes transaminitis and/or direct hyperbilirubinemia. Pancreaticobiliary anomalies

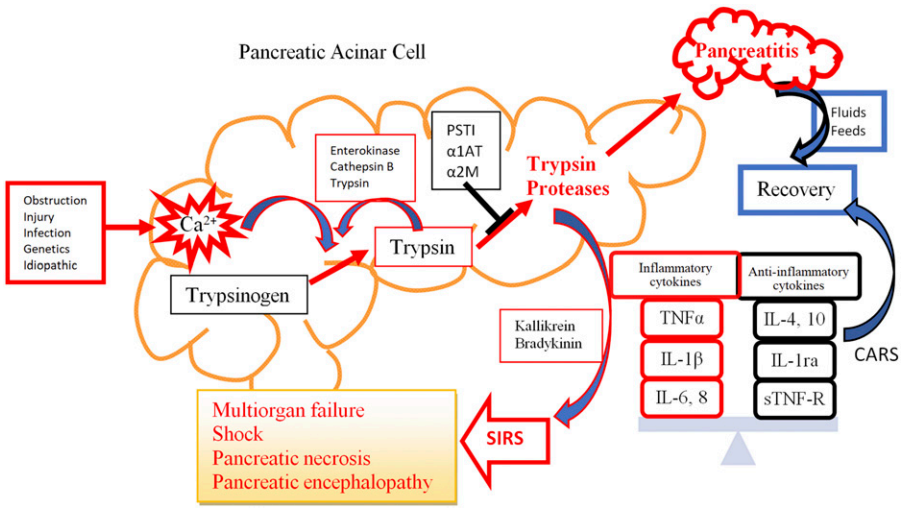

Figure 1. Pancreatic acinar cell. The diagram shows the initial insult, which leads to an inappropriate rise in intracellular calcium that triggers the activation of trypsin and other digestive proenzymes, which in turn stimulate inflammatory cytokines, leading to systemic inflammatory response syndrome (SIRS) and pancreatitis. Protective mechanisms include the inhibitory factors, including pancreatic secretory trypsin inhibitor (PSTI), alpha-1 antitrypsin (α1AT), α2-macroglobulin (α2M), and compensatory anti-inflammatory response syndrome (CARS). IL=interleukin, TNF=tumor necrosis factor.

Table 1. Etiology of Pancreatitis in Children and Adolescents

COMMON BILIARY DISORDERS	LESS COMMON INFECTIONS	RARE AUTOIMMUNE
- Cholelithiasis	- Viral: mumps, measles, coxsackievirus, echovirus, influenza, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, varicella zoster virus	- Type 1 autoimmune pancreatitis
- Biliary sludge	- Bacterial: *Mycoplasma pneumoniae*, *Salmonella* spp, gram-negative bacteria	- Type 2 autoimmune pancreatitis
- Choledochal cyst		- Primary sclerosing cholangitis
- Caroli disease (rare)		
Systemic conditions	Metabolic disorders (17)	Anatomical
- Sepsis/shock	- Diabetic ketoacidosis	- Pancreaticobiliary junction malunion
- Hemolytic uremic syndrome	- Hyperlipidemia	- Annular pancreas
- Inflammatory bowel disease	- Organic acidemia	- Pancreas divisum
- Systemic lupus erythematosus	- Hypercalcemia	- Sphincter of Oddi dysfunction
- Juvenile idiopathic arthritis	- Alpha-1 antitrypsin deficiency	
- Polyarteritis nodosa	- Long-term total parenteral nutrition	
- Henoch-Schonlein purpura		
- Kawasaki disease		
- Cystic fibrosis		
- Celiac disease		
Medications (8)(18)	Genetic/hereditary disorders: 34 gene mutations	Nutrition
- L-asparaginase/cytarabine/vincristine	- *CFTR*	- Malnutrition
- Valproic acid/carbamazepine	- *SPINK1*	- Vitamin A and D deficiency
- Azathioprine/6-mercaptopurine	- *PRSS1*	
- Mesalamine	- *CTRC*	
- Sulfamethoxazole/trimethoprim	- *CASR, CEL, CLDN2, CPA1, SBDS, UBR1*	
- Calcium carbonate		
- Indomethacin		
- Isoniazid		
- Estrogen/corticosteroid		
- Furosemide		
Trauma		
- Blunt injury		
- Child abuse		
- Endoscopic retrograde cholangiopancreatography		
Idiopathic		

increase the risk of pancreatitis, such as pancreas divisum, (19)(20) choledochocyst, or, rarely, Caroli disease, which is characterized by cystic dilation of hepatic bile ducts.

IDIOPATHIC. Approximately 13% to 34% of pancreatitis cases are reported as idiopathic. However, this statistic continues to decrease as genetic data for previously diagnosed idiopathic cases emerge. (21)

SYSTEMIC CONDITIONS. The reported case association between AP and systemic illness ranges from 3.5% to 48%. (22) Commonly described systemic conditions associated with an increased risk include sepsis, shock, hemolytic uremic syndrome, systemic lupus erythematosus, juvenile idiopathic arthritis, celiac disease, and inflammatory bowel disease, especially with the association of primary sclerosing

cholangitis. (23) Cystic fibrosis, leading to inspissated bile and pancreatic fluids in pancreaticobiliary ducts, may present with pancreatitis. Vasculitides such as polyarteritis nodosum, Henoch-Schonlein purpura, and Kawasaki disease have also been linked to pancreatitis.

MEDICATIONS. Drug-induced pancreatitis is due to different mechanisms depending on the medication, including immunologic reactions (eg, 6-mercaptopurine, amino salicylates), accumulation of toxic metabolites, ischemia (eg, diuretics), intravascular thrombosis (eg, estrogen), and increased viscosity of a pancreatic juice (eg, glucocorticoids). (8)(18)

TRAUMA. Trauma should always be considered as an etiology for AP. Examples of trauma associated with pancreatitis include blunt injury, child abuse, and instrumentation of the pancreaticobiliary junction and pancreatic ducts via endoscopic retrograde cholangiopancreatography (ERCP).

INFECTIONS. Many infections have been associated with pancreatitis, including viruses such as mumps, measles, coxsackievirus, echovirus, influenza, hepatitis A, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella zoster virus. Bacterial etiologies for pancreatitis include *Mycoplasma pneumoniae*, *Salmonella*, and gram-negative bacteria.

METABOLIC DISEASES. Several metabolic diseases are associated with AP. A few etiologies include diabetic ketoacidosis, hyperlipidemia, organic acidemias such as methylmalonic academia, hypercalcemia, and alpha-1 antitrypsin deficiency. (17) Prolonged total parenteral nutrition (TPN) may not only predispose children to AP but also trigger acute episodes in patients with CP.

GENETIC DISORDERS. With advancements in gene sequencing, genetic variants associated with pancreatitis are becoming increasingly important factors for understanding the pathophysiology of pediatric pancreatitis. (24) Studies have identified mutations in genes involved in premature intrapancreatic activation of trypsin (*CFTR, PRSS1, PRSS2, SPINK1, CTRC, CTSB, KRT8, CASR*), in calcium signaling and zymogen exocytosis (*ATP2C2, STIM, TRPV6, DMBT1, TRP*), in pancreatic secretion and ion homeostasis (*CLPS, F2RL1, SLC4A2, RAP27B, CPB1, SLC4A4, SLC26A3, TMPRSS15, UBR1, SBDS*), and in the autophagy pathway (*HSP90AA1, LAMP2, MAP1LC3B*). Other newly discovered potential pancreatitis susceptibility genes include *CPA1,* (25) *CLDN2,* (26) and *CEL.* (27) Although up to 34 gene mutations have been associated with ARP and CP, mutations of *CFTR* and *PRSS1* occur at the highest rate in idiopathic ARP and CP, respectively. (21)(28)(29)(30) As specific mutations predispose an individual to ARP and CP, genetic testing is recommended for recurrent AP and/or an isolated AP event in the setting of family history of AP or CP. Initial screenings should focus on the most common pathogenic variants, which include *PRSS1, SPINK1, CTRC, CPA1, CFTR,* and the *CEL* hybrid. Genetic findings aid in long-term prognosis, especially since hereditary pancreatitis associated with *PRSS1* mutations have been linked to increased risk of pancreatic adenocarcinoma. (31)

AUTOIMMUNE PANCREATITIS. Autoimmune pancreatitis (AIP), a rare cause of pediatric pancreatitis, is defined by pancreatic parenchymal changes that are clinically responsive to corticosteroids. (32) AIP occurs as either type 1 or type 2. Type 1 is associated with elevated immunoglobulin G4 levels, diffuse narrowing of the main pancreatic duct, segmental enlargement of the pancreas, and/or strictures of the lower bile duct. (33) However, normal immunoglobulin G4 levels do not rule out AIP. Type 2 is more common in children and is associated with inflammatory bowel disease and other autoimmune processes. (34)

ANATOMICAL. The pancreas may be predisposed to pancreatitis due to congenital anatomical abnormalities such as pancreaticobiliary junction malunion, which creates an environment causing poor flow of the pancreatic fluids in the abnormal duct. Annular pancreas is a congenital anomaly that may increase the risk of pancreatitis. Pancreas divisum and sphincter of Oddi dysfunction can result in inadequate pancreatic secretion drainage, resulting in pancreatitis.

Diagnosis

SYMPTOM CRITERIA. In pediatrics, 68% to 95% of patients with AP present with abdominal pain, (14)(35) 62% to 89% are localized to the epigastric region, and 1.6% to 5.6% have associated radiating back pain. (36)(37) In contrast, infants and toddlers present more commonly with irritability and vomiting. (22) The pain associated with pancreatitis stems from multiple mechanisms, including stimulation of visceral pancreatic and somatic peritoneal pain receptors by inflammatory cytokines. (38) Elevated pressures in the pancreatic system leading to ischemia and activation of primary sensory neurons are other mechanisms for abdominal pain during pancreatitis. (39)

BIOCHEMICAL CRITERIA. Although amylase and/or lipase levels are used to diagnose pancreatitis, an elevated serum lipase level is more sensitive than amylase level for diagnosis. (6)(14) Serum amylase and lipase levels are elevated in 50% to 85% and 77% to 100% of pediatric patients, respectively. (19)(22)(35)(37)(40) Serum amylase levels rise within 6 to 12 hours and fall within 3 to 5 days. The differential diagnosis for hyperamylasemia includes salivary gland conditions, intestinal etiologies such as obstruction,

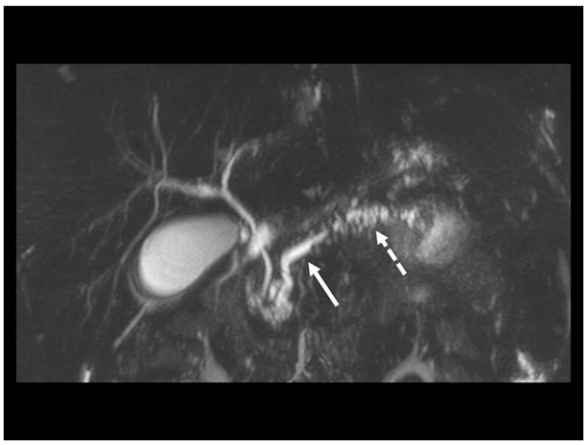

Figure 2. Three-dimensional maximum-intensity projection from a magnetic resonance cholangiopancreatography examination in an 11-year-old patient with chronic pancreatitis. The main pancreatic duct is dilated (solid white arrow), with significant irregularity. The irregularity is most pronounced in the area of the pancreatic tail (dashed arrow), where there are also multiple dilated side branch ducts.

peptic ulcers, appendicitis, celiac disease, gastroenteritis, and eating disorders. Conversely, an elevated serum lipase level can be seen as early as day 1 of illness, persists for 14 days, and is pancreatic specific. Serum triglyceride and calcium levels should be measured with the first episode of AP to rule out hypertriglyceridemia or hypercalcemia as potential etiologies. (1)

IMAGING. The diagnostic features of AP on imaging studies include evidence of biliary obstruction, parenchymal changes, and peripancreatic fluid collections. Controlled trials on the use of imaging tools have yet to be performed in children. (1) Transabdominal ultrasonography (TUS) is the recommended initial imaging study for suspected AP, with an effectiveness rate of 56% to 84% in pediatric patients with AP. (41) TUS is advantageous because it lacks ionizing radiation, is effective for the identification of gallstones and pancreatic fluid collections, and comparatively costs less than other modalities.

Although not yet widely used in children due to its availability, endoscopic ultrasonography (EUS) is an effective tool to recognize biliary pancreatitis or pseudocysts in children greater than 5 years old. (42) In a study looking at 11,000 pediatric EUS procedures, indications, and outcomes, the authors underscored that EUS indications in children are comparable with those in adults. Furthermore, the findings significantly contributed to the diagnosis and treatment of pediatric pancreaticobiliary disease. (43)

Magnetic resonance cholangiopancreatography (MRCP) is the imaging method of choice for diagnostic evaluation of the pancreaticobiliary system in children and is recommended by the INSPPIRE consensus when TUS is suggestive of AIP (32) or in pediatric ARP and CP. (5) It carries less risk than ERCP and is highly sensitive in detecting congenital ductal abnormalities, choledocholithiasis, strictures, pancreas divisum, and pancreatic and biliary tumors. (44)(45) Figures 2 and 3 present MRCP images from an 11-year-old with CP due to *PRSS1* mutation demonstrating pancreatic duct stricture with intermittent dilation, so-called beading, of the duct.

Contrast-enhanced abdominal computed tomography is not first-line imaging due to radiation exposure but is best suited for situations of diagnostic uncertainty and clinical deterioration, such as necrosis and bleeding in clinically severe AP. The optimal timing for detecting inflammatory changes surrounding the pancreas by computed tomography is at least 72 to 96 hours after initial AP presentation. (46)

ERCP is available in some pediatric centers and may be combined with EUS where available. (47)(48) ERCP should be used only for therapeutic purposes due to the risks associated with ERCP, such as bleeding, perforation, and pancreatitis. In particular, the risk of pancreatitis after ERCP was reported to be 9.7%. (47)(48)

Management

FLUID RESUSCITATION. Aggressive fluid resuscitation is a mainstay in the acute management of AP. It addresses hypovolemia, increases pancreatic perfusion, improves microcirculation, and reduces the risk of necrosis. Both normal saline and lactated Ringer solution (LR) have been studied. In an adult study, compared with normal saline, LR was shown to significantly decrease the incidence of SIRS (49) and the development of post-ERCP pancreatitis. (50) However, another study found no difference between LR and normal

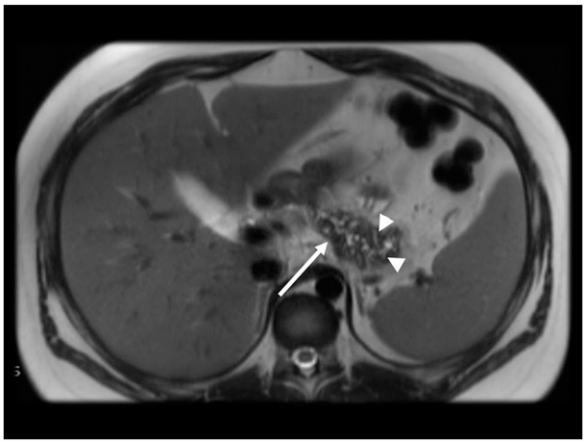

Figure 3. Axial T2 HASTE (half-Fourier acquired single-shot turbo spin-echo) image at the level of the pancreatic tail demonstrating significant atrophy of the pancreatic parenchyma (solid white arrow) along with multiple dilated side branch ducts (arrowheads).

Table 2. Management Recommendation Summary

PAIN	FLUIDS	NUTRITION	ANTIBIOTICS
Acetaminophen	LR or D5W NS at 1.5 to 2× maintenance rate	Oral feeding within 24–48 h of admission	Only indicated for cholangitis or necrotizing pancreatitis
Ibuprofen	Initiate within 24 h of presentation	Nasogastric/nasojejunal feedings if not tolerating oral feeds	Carbapenems, quinolones, or metronidazole
Opioids	Monitor BUN/creatinine and urine output for 24–48 h	Parenteral nutrition if not tolerating enteral feeds	
		Feed normal diet if eating	
		Polymeric formula (if no food allergies)	

BUN=blood urea nitrogen, D5W=dextrose 5% in water, LR=lactated Ringer solution, NS=normal saline.

saline when looking at mortality and duration of hospital stay. (51) Current recommendations are for initiation of therapy with dextrose-containing crystalloids (1) or LR (2) at 1.5 to 2 times maintenance within 24 hours (Table 2). (47) Notably, pediatric studies have demonstrated an association between aggressive fluid administration and fewer ICU admissions, shortened hospital stays, and higher rates of clinical recovery. (52)(53)

PAIN. There is no specific pain management guideline for pediatric AP or quality data on differences between analgesics. Acetaminophen and ibuprofen are the first-line agents for mild pain, and opioids are indicated for severe pain. Although opioids increase the sphincter of Oddi tone, clinical studies do not correlate this with poor outcomes. A Cochrane review assessing the efficacy and safety of opioid use found that it is appropriate in the treatment of pain related to AP and that its use may decrease the need for supplementary analgesia. (54) However, a retrospective review of 211 pediatric patients with AP at the Boston Children's Hospital Emergency Department found that opioid analgesia was more frequently prescribed than nonopioid alternatives, time to analgesia was shorter in opioid-receiving patients, and they required more doses of analgesics. (55)

Procaine, a local anesthetic that is administered systemically, has been considered for basic analgesia for AP. One controlled trial showed the effectiveness of systemic administration of procaine in pancreatitis, with accelerated postoperative recovery, improved cognitive function, and overall shortened hospital stay. (56) Epidural anesthesia, used as a sympathetic nerve block that redistributes blood flow to nonperfused pancreatic regions, has shown improved pancreatic perfusion, decreased AP pain, and the need for necrosectomy. (57)

NUTRITION. Guidelines for pediatrics have been extrapolated from adult data and consensus from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. (2)(3) Enteral feeding within 24 to 48 hours of pancreatitis onset is recommended. Multiple studies support early feeding with a regular diet in mild AP because early feeding can reduce the length of stay. (2)(3) Remaining nil per os or on a clear liquid diet does not improve abdominal pain. If a patient cannot tolerate an oral diet, nasogastric or nasojejunal enteral formula feeding is recommended. Initiation of feedings is not dependent on the severity of pancreatitis, and studies have not demonstrated a difference between nasogastric and nasojejunal feedings. Likewise, polymeric formula is appropriate first-line nutrition. TPN is reserved for when enteral nutrition cannot be tolerated, such as pancreatic fistulae, perforated pancreatic duct, ileus, or abdominal compartment syndrome. The risks of central line infections secondary to bacterial translocation increase with TPN in the setting of AP. (1)

ANTIBIOTICS. Prophylactic antibiotics are not recommended in AP, even in the presence of severe AP or existing necrosis, because most are sterile. Indications for antibiotics include systemic infectious complications, cholangitis, and suspected infected pancreatic necrosis. In the setting of persistent systemic inflammatory response beyond the first week of symptom onset, ultrasonography-guided fine-needle aspiration could differentiate infected and sterile pancreatic necroses. Imipenem, meropenem, fluoroquinolones, and metronidazole exhibit effective tissue penetration and bactericidal properties for infected pancreatic necrosis and prevention of septic complications. (58)(59) Antibiotics ideally are used in conjunction with surgical or percutaneous drainage.

BILIARY AP MANAGEMENT. ERCP is indicated in the setting of choledocholithiasis, biliary duct sludge causing biliary pancreatitis, cholangitis, and biliary or pancreatic duct obstruction (Fig 4). Procedures performed with ERCP in pediatric patients include biliary or pancreatic sphincterotomy, stent placement, stricture dilation, and transmural drainage of cysts. One study showed that therapeutic ERCP is

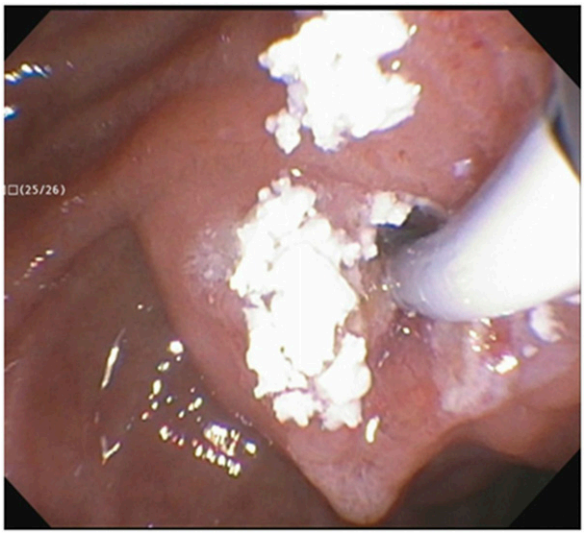

Figure 4. Multiple pancreatic duct stones extracted during endoscopic retrograde cholangiopancreatography after sphincterotomy in an 11-year-old patient with chronic hereditary pancreatitis.

frequently used in children with ARP or CP because both are associated with pancreaticobiliary obstruction. (60) ERCP should be completed within 24 hours in patients with severe cholangitis. Pancreatic fluid collection and pseudocysts are common complications of AP, occurring in approximately 58% and 38% of children with AP, respectively. (61) Interventional EUS is used for visualization to drain pancreatic pseudocysts. (62)(63)

Complications

Localized complications include the development of pseudocysts, pancreatic necrosis, and abscesses. A pseudocyst is a homogenous collection of amylase-rich pancreatic fluid surrounded by granulation tissue. The cysts take approximately 30 days to develop and can be complicated by infection or hemorrhage, resulting in pancreatic ascites. Of note, if compensatory anti-inflammatory response syndrome is excessive in the inflammatory cascade, inhibition of new cytokine production can lead to increased susceptibility to sepsis, infectious necrosis, and pancreatic abscess.

The systemic complications are vast, can be devastating in pancreatitis, and may include multiorgan system failure, shock, gastrointestinal bleeding, splenic artery pseudoaneurysms, splenic infarction, intestinal obstruction, and perforation. In addition, cardiorespiratory, metabolic, and renal complications may occur, including acute respiratory distress syndrome, pleural effusion, pericardial effusion, myocardial dysfunction, acute renal failure, hypermetabolic state, hypocalcemia, disseminated intravascular coagulation, and ascites.

ACUTE RECURRENT PANCREATITIS

There is a 10% to 35% chance of AP recurrence after the initial episode. (35) Risk factors play a major role in the development of ARP and CP. Identified risk factors, similar to AP, include genetic mutations, obstructions, toxic/metabolic disorders, and autoimmune processes (Table 1).

Previously, Giefer et al (64)(65) detected pancreatitis-associated genetic mutations (*PRSS1*, *CFTR*, *SPINK1*, or *CTRC*) in 71% of children with early-onset pancreatitis, which is defined as occurring before 6 years of age. Meanwhile, a smaller percentage of such mutations was detected in children12 years and older with ARP or CP. These differences in age suggest external triggers, such as hypertriglyceridemia, autoimmune diseases, metabolic diseases, or medications as more likely etiologies for ARP in older children. (64)(65)

CHRONIC PANCREATITIS

CP is an irreversible inflammatory process that results in morphologic changes, such as stricture, atrophy, and pseudocysts, or impaired exocrine or endocrine pancreas function as a consequence of ARP. (5) CP is most often diagnosed clinically with the aid of laboratory and imaging studies rather than by histopathologic analysis. Genetic etiologies are common for pediatric CP, although recurrent or prolonged obstruction, trauma, chronic toxins such as TPN, and systemic diseases such as AIP are all possible etiologies. A sweat chloride test should be performed as part of the diagnostic evaluation of CP to rule out cystic fibrosis. AP in the setting of CP is treated essentially the same, with aggressive fluid management, pain control, and early feeding. If the patient demonstrates pancreatic exocrine insufficiency, then pancreatic enzyme replacement therapy may be used with enteral feeding for improved absorption.

In pediatric patients with CP, a normal diet is recommended, consisting of 35% to 40% fat, 20% protein, and 40% to 45% carbohydrates, between acute episodes. Patients with CP should be evaluated for pancreatic exocrine insufficiency and fat malabsorption via fecal pancreatic elastase-1 or 72-hour fecal fat test. Every 6 to 12 months they should have their weight, height, body mass index, and fat-soluble vitamins A, D 25-OH, E, and K measured. If supplementation is required, repeated levels should be drawn after 3 months. There is no evidence supporting routine monitoring of trace elements or water-soluble vitamins. Although there are no data on bone mineral density in children, the consensus recommendation is that bone mineral density should be assessed in children with CP presenting with low vitamin D 25-OH levels, fractures, or malnutrition.

Pain control should be managed with nonopioid therapies while also ruling out continued injury if there is an acute exacerbation of pain. The use of pancreatic enzyme replacement therapy for pain control is controversial, with a recent systematic review in adults showing it to be ineffective. (66) In CP, pain control is aimed at treating the neuropathic nature of the pancreatic pain. In particular, the current literature supports the use of selective serotonin reuptake inhibitors, pregabalin, or gabapentin; however, no studies have evaluated the efficacy of these medications in children with CP. (67)

The scope of this review is not sufficient to fully explore the surgical options. Surgery is indicated in patients with chronic debilitating pain, chronic malnutrition due to pancreatic exocrine insufficiency, malabsorption despite nutritional rehabilitation, and/or diabetes. In addition to the traditional surgical options to provide pancreatic drainage, there is growing evidence for management of pediatric CP with pancreatectomy and islet cell autotransplant, with favorable results for pain resolution and nutritional outcomes. (68)

Summary

With the advent of the INSPPIRE collaborative, improved imaging, increased numbers of pediatric interventional endoscopists trained in ERCP and EUS, and increased genetic testing, much has changed in the field of pediatric pancreatitis in the past several years. However, further research is desperately needed regarding the specific etiologies and the optimal fluid, nutrition, and interventional management of pediatric pancreatitis. At this time, the key changes to management include early enteral nutrition within 24 hours and avoidance of nil per os/TPN due to decreased morbidity associated with enteral nutrition. Nutrition may be oral, nasogastric, or nasojejunal depending on the clinical scenario. IV fluid management with LR may be superior to normal saline, but studies in children are lacking. Prophylactic antibiotics are not warranted for pancreatitis, including severe or necrotic AP unless the pancreas is proved to be infected via convincing clinical evidence or diagnostic tests. Finally, additional studies are needed to assess pain management to identify the optimal minimal opioid therapy.

Suggested Quality Improvement Projects

- Methods to reduce length of stay in patients with pancreatitis.
- Evaluation of efficacy of LR versus normal saline in pediatric pancreatitis.
- Role of diet or dietary supplements in recurrent attacks of pancreatitis.
- Monitoring practices to identify risk factors and detect early growth and nutritional deficiencies in CP.
- Prospective analysis of AP pain management with objective measures to help curb the opioid epidemic.

References for this article can be found at http://pedsinreview.aappublications.org/content/41/No. 10/511.

PIR QUIZ

Individual CME quizzes are available via the blue CME link under the article title in the online Table of Contents of any issue. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

1. You are asked to do a consultation of a previously healthy 16-year-old boy with acute abdominal pain. His pain is localized to the epigastric region and has worsened over the past 2 days. He experienced 1 episode of nonbilious, nonbloody emesis. No fever or change in stool pattern was noted. He takes no medications. He denies alcohol use. Family history is negative for any chronic conditions. He is an A and B student and plays offensive tackle for his high school football team. On physical examination he appears uncomfortable but is in no distress. His BMI is at the 95th percentile. Abdominal examination shows tenderness over the epigastric region, with soft and nontender lower quadrants and no organomegaly. Results of laboratory studies, including a complete blood cell count and a complete metabolic panel, are normal except for an amylase level of 1,240 U/L (20.7 μkat/L) and a lipase level of 860 U/L (14.4 μkat/L). Abdominal ultrasonography findings are normal. He is diagnosed as having acute pancreatitis. This is the third case you have seen in the past 6 months. After 22 years in practice, you are curious why you are seeing more cases of this condition. Which one of the following factors has been linked to the increasing prevalence of acute pancreatitis in the past 2 decades?

   A. Binge drinking.
   B. E-cigarette use.
   C. Lead exposure.
   D. Obesity.
   E. Vegetarian diet.

2. You are asked to see a 12-year-old girl presenting with her third episode of acute pancreatitis in the past 8 months. Previous testing for her first episode of acute pancreatitis included normal liver function test results, lipid profile, immunoglobulin subclasses, and abdominal ultrasonography. She presents with acute abdominal pain, intermittent vomiting, and biochemical features similar to her previous presentations. On physical examination she appears uncomfortable and is frustrated that this is happening again. Her BMI is at the 50th percentile and she appears well nourished. She experienced no interval weight loss since her last episodes of pancreatitis. Abdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP) are normal. Which one of the following is the most appropriate test to obtain to help identify the cause predisposing this patient to recurrent pancreatitis?

   A. Endoscopic retrograde cholangiopancreatography (ERCP).
   B. Fecal elastase.
   C. Genetic testing.
   D. Ultrasonography-guided pancreatic needle biopsy.
   E. Urine drug screen.

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3. An 8-year-old boy is admitted with his second episode of acute pancreatitis. Similar to the first episode, he experienced 3 days of increasing abdominal pain and intermittent nonbloody, nonbilious emesis. On physical examination he is uncomfortable but in no distress. He is not jaundiced and there are no excoriations to suggest pruritus. The epigastric area is tender to palpation, but the lower quadrants are soft. Laboratory values are as follows: hemoglobin, 14.8 g/dL (148 g/L); white blood cell count (WBC), 16,300 (16.3×10^9/L); sodium, 140 mEq/L (140 mmol/L); carbon dioxide, 21 mEq/L (21 mmol/L); blood urea nitrogen (BUN), 16 mg/dL (5.7 mmol/L); creatinine, 0.9 mg/dL (79.6 μmol/L); total bilirubin, 2.8 mg/dL (47.9 μmol/L); conjugated bilirubin, 0.2 mg/dL (3.4 μmol/L); aspartate aminotransferase (AST), 53 U/L (0.89 μkat/L); alanine aminotransferase (ALT), 82 U/L (1.37 μkat/L); γ-glutamyltransferase (GGT), 115 U/L (1.92 μkat/L); amylase, 940 U/L (15.7 μkat/L); and lipase, 1,020 U/L (17.03 μkat/L). Ultrasonography findings are normal. Which one of the following is the next best imaging test recommended to be performed to evaluate the pancreaticobiliary system in this patient?

   A. Contrast-enhanced computed tomography.
   B. Exploratory laparoscopy.
   C. Endoscopic ultrasonography.
   D. Hepatobiliary scintigraphy.
   E. MRCP.

4. You are seeing a 15-year-old boy in your office for emergency department follow-up. He presents with a 5-day history of increasing abdominal discomfort and nausea without vomiting. There has been no change in his stool pattern, but he is not urinating as frequently as normal. He was seen in the emergency department 2 days ago, where laboratory studies included a normal complete blood cell count and urinalysis findings. A comprehensive metabolic panel included normal electrolyte, BUN, and creatinine levels, but the AST and ALT levels were 62 U/L (1.04 μkat/L) and 86 U/L (1.44 μkat/L), respectively. A trial of over-the-counter antacid therapy did not relieve the discomfort. On physical examination he is mildly tachycardic and appears uncomfortable and tired. Mucous membranes are tacky. Capillary refill is less than 2 seconds. There is no jaundice or scleral icterus. The epigastric area is tender, but there is no organomegaly and the lower quadrants are soft. You decide to admit him to the hospital for further evaluation and management. Laboratory studies showed the following values: hemoglobin, 17 g/dL (170 g/L); WBC, 12,400 (12.4×10^9/L); sodium, 145 mEq/L (145 mmol/L); carbon dioxide, 19 mEq/L (19 mmol/L); BUN, 25 mg/dL (8.9 mmol/L); creatinine, 1.2 mg/dL (106.1 μmol/L); triglycerides, 120 mg/dL (1.36 mmol/L); cholesterol, 60 mg/dL (1.55 mmol/L); AST, 80 U/L (1.34 μkat/L); ALT, 95 U/L (1.59 μkat/L); GGT, 66 U/L (1.10 μkat/L); amylase, 1,430 U/L (23.88 μkat/L); and lipase, 1,080 U/L (18.04 μkat/L). On urinalysis the specific gravity was 1.021; pH 6.5; and negative for white or red blood cells, leukocyte esterase. Abdominal ultrasonography findings are normal. After he received 10 mL/kg of normal saline, lactated Ringer solution at twice his maintenance fluid rate was given overnight. The next morning he reports that he is feeling better but continues to experience significant epigastric abdominal pain despite analgesics. Liver tests, amylase, lipase, BUN, and creatinine levels are decreasing. Which one of the following is the best recommendation to address his nutritional needs for the day?

   A. Clear liquids.
   B. Mechanically soft diet.
   C. Nothing by mouth.
   D. Regular diet.
   E. Total parenteral nutrition.

5. A 14-year-old girl is admitted to the hospital with her fourth episode of acute pancreatitis in 2 years. Results of diagnostic studies, including magnetic resonance imaging, ERCP, a lipid panel, autoimmune markers, sweat chloride test, genetic testing, and immunoglobulin subclasses, have been negative or normal. You are concerned that she now may have chronic pancreatitis. Which one of the following study results is most likely to support the diagnosis of chronic pancreatitis?

   A. Elevated amylase and lipase levels.
   B. Elevated erythrocyte sedimentation rate.
   C. Elevated fecal alpha-1 antitrypsin level.
   D. Low fecal pancreatic elastase-1 level.
   E. Low serum ionized calcium level.

Sexually Transmitted Infections Part 2: Discharge Syndromes and Pelvic Inflammatory Disease

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EDUCATION GAPS

Pediatricians should be able to diagnose and manage patients presenting with a vaginal discharge and the symptoms of pelvic inflammatory disease (PID). Providers should be aware that chlamydia is often asymptomatic in females and that gonorrhea may be resistant to traditional treatment. They should know the newer diagnostic techniques for sexually transmitted infections (STIs), recent Centers for Disease Control and Prevention (CDC) guidelines for the treatment of STIs and PID, and the indications for hospitalization.

OBJECTIVES *After completing this article readers should be able to:*

1. Identify the presentation of sexually transmitted infections (STIs) with a vaginal discharge, including the symptoms of pelvic inflammatory disease (PID).
2. Understand the evaluation, differential diagnosis, and diagnostic techniques for common STIs, such as chlamydia, gonorrhea, trichomonas, and PID.
3. Plan the management of these STIs and PID using the most recent Centers for Disease Control and Prevention (CDC) treatment guidelines. (3)
4. Be familiar with the indications for hospitalization in patients with PID.

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ABBREVIATIONS

BV	bacterial vaginosis
CDC	Centers for Disease Control and Prevention
EPT	expedited partner treatment
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IM	intramuscularly
IUD	intrauterine device
IV	intravenous
KOH	potassium hydroxide
MSM	men having sex with men
NAAT	nucleic acid amplification test
PID	pelvic inflammatory disease
STD	sexually transmitted disease
STI	sexually transmitted infection
VVC	vulvovaginal candidiasis

ABSTRACT

Sexually transmitted infections (STIs) disproportionately affect young people, with more than half of the infections occurring in youth aged 15 to 25 years. (1)(2) This review, the second in a 2-part series on STIs, focuses on infections that may cause abnormal vaginal or penile discharge, including trichomonas, chlamydia, gonorrhea, and pelvic inflammatory disease (PID). Most infected persons, however, are asymptomatic. Nucleic acid amplification tests are the most sensitive and specific for the detection of chlamydia, gonorrhea, and trichomoniasis, and they can be performed on provider- or patient-collected

swabs. Providers should have a low threshold for diagnosing and treating PID because untreated PID can have serious long-term complications for young women. Indications for hospitalization for PID include the presence of a tubo-ovarian abscess, severe illness with systemic symptoms, pregnancy, human immunodeficiency virus infection, and failure to respond to outpatient oral treatment (within 48–72 hours) or inability to tolerate the oral treatment.

Common sexually transmitted infections (STIs) in adolescents fall into 3 diagnostic groups: genital bumps, genital ulcers, and discharge syndromes. This review is the second in a 2-part series. For further information regarding primary and secondary prevention of all STIs and the discussion of STI syndromes that present as genital bumps or genital ulcers, please see "Sexually Transmitted Infections Part I: Genital Bumps and Genital Ulcers" (*Pediatrics in Review,* September 2020). This review addresses the diagnosis and management of discharge syndromes and pelvic inflammatory disease (PID) using a case-based approach.

CASE (VERSION 1)

A 17-year-old girl presents to the office with a complaint of a "bad smell" and some genital pruritus. She has had some profuse, foul-smelling vaginal discharge on her underwear for the past week. She states that she has had vaginal intercourse a few times during the past month with a single male partner using a condom every time except once. Her last period was 2 weeks ago. She denies abdominal pain or dysuria. She recently completed a course of antibiotics for a sinus infection. A decision is made to perform a pelvic examination, collect samples, and perform microscopy of the vaginal discharge.

On Examination

The patient is well-appearing and has no abdominal or suprapubic tenderness. On speculum examination a frothy, yellow discharge is seen in the vagina, and the cervix appears red and irritated. She has some discomfort with the examination but does not have acute cervical motion tenderness or adnexal tenderness.

Vaginal swab specimens for nucleic acid amplification testing (NAAT) for chlamydia and gonorrhea and specimens for Gram-stain and culture for *Trichomonas* antigen are obtained. In addition, 2 cotton-tipped swabs are used to obtain vaginal secretions. These are then used to prepare 2 slides (wet preps): one with normal saline and the other with 10% potassium hydroxide (KOH) for viewing under the microscope. Vaginal pH is also checked using a pH paper swabbed with secretions from the vagina and is found to be 6.5. A pregnancy test is negative.

On Microscopy

A fishy odor is noted when the vaginal swab is dipped in the KOH on the slide. Microscopy reveals multiple clue cells, numerous polymorphic nucleocytes, and a few motile flagellated organisms.

Diagnosis

Trichomonas vaginalis and bacterial vaginosis (BV).

Treatment

A decision is made to treat with a single dose of metronidazole 2 g orally, explaining to the patient the possible adverse effects of the medication, including the risk of a disulfiram-like reaction if alcohol is consumed while taking metronidazole. The patient is also advised that because trichomoniasis is sexually transmitted, her partner should also be treated. Expedited partner treatment (EPT) is offered to the patient, and consistent condom use is reinforced. The patient is also advised that she and her partner should not resume sexual activity until both are treated and asymptomatic. The patient is informed that she also has BV and that the recommended therapy will treat both infections. She is told that BV is not sexually transmitted but can recur and that treatment of partners has not been shown to prevent recurrences. The importance of screening for other STIs, including human immunodeficiency virus (HIV), is also discussed, and information about contraceptive methods and emergency contraception is offered to the patient.

CAUSES OF VAGINAL DISCHARGE

Vaginal discharge can be caused by vaginitis or cervicitis. The most common causes of vaginitis are vulvovaginal candidiasis (VVC)/yeast vaginitis (not sexually transmitted), trichomoniasis (sexually transmitted), and BV (not usually sexually transmitted). Cervicitis is usually caused by chlamydia or gonorrhea.

TRICHOMONIASIS

What Causes Trichomoniasis?

Trichomoniasis is caused by *T vaginalis*, an anaerobic, flagellated protozoan parasite.

Epidemiology

Approximately 3.7 million individuals are infected with *T vaginalis,* making it the "most prevalent non-viral curable, sexually transmitted infection" in the United States. (1) The prevalence is higher in African American women (13%) compared with non-Hispanic white women (1.8% affected). (4) Disparities in rates of STIs are often due to broader inequities in social and economic conditions for minority communities. (2) Trichomoniasis is more prevalent in older adolescents and those who are incarcerated, have other STIs or BV, or use illicit drugs. (3) Patients presenting to sexually transmitted disease (STD) clinics also have a higher prevalence of *T vaginalis* infections. (5)

Signs and Symptoms

Symptomatic women usually have a profuse, yellowish greenish, malodorous vaginal discharge with occasional vulvar irritation. Speculum examination may reveal a cervix with petechiae, an appearance called a "strawberry cervix" (Fig 1). Males have symptoms of urthritis, epididymitis, or prostatitis. (6) Approximately 80% of infected persons are asymptomatic. (1)(3) Acquisition of HIV is higher in individuals infected with *T vaginalis,* and those who are co-infected will be more likely to increase shedding of the HIV virus. (7)

When to Test?

Asymptomatic screening: Screening should be considered for all high-risk individuals (multiple sex partners, men who have sex with men [MSM], history of another STI, HIV positive, and those who present to STD clinics).

Symptomatic screening: All women who present with a vaginal discharge should be tested for *T vaginalis*. (3) The Centers for Disease Control and Prevention (CDC) does not recommend rectal and oral testing for *T vaginalis.*

Recommended Tests

Wet mount: In clinics with approved microscopy, a wet preparation with visualization of motile trichomonads is diagnostic. Wet mount, however, is observer-dependent and has sensitivity of only 51% to 65%. (8) If stored in normal saline the specimen can be examined within an hour, but once a slide is prepared it must be examined within 10 minutes (Fig 2).

Culture: Culture of urine sediment or urethral swab can be performed in men, but in women culture can be performed only on vaginal secretions. (3) Culture is rarely used since the development of more sensitive/specific tests.

NAAT: The most sensitive/specific test is the APTIMA® *T vaginalis* assay (Hologic Inc, Marlborough, MA), which has been approved by the Food and Drug Administration (FDA) for the detection of *Trichomonas* from vaginal swabs (provider- or patient-collected), endocervical swabs, or urine specimens from women (sensitivity, 95.3%–100%; specificity, 95.2%–100%) and from urine or urethral swabs from men. (9)(10)

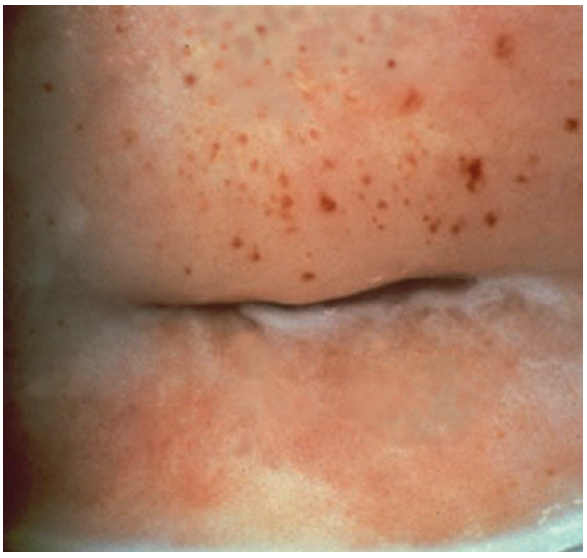


Figure 1. Multiple petechiae on the cervix of a women with trichomoniasis, often referred to as a strawberry cervix. (Reprinted with permission from the National STD Curriculum. Source of original image: Claire Stevens, University of Washington.)

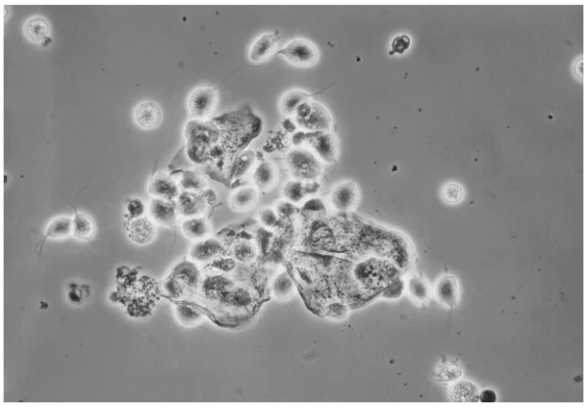


Figure 2. Wet prep photomicrograph shows several *Trichomonas vaginalis* protozoan parasites, oval in shape with thin flagella. (Reprinted with permission from the Centers for Disease Control and Prevention's Public Health Image Library. Source of original image: Joe Millar, 1975.)

Rapid tests: Point-of-care testing includes the OSOM® rapid antigen detection test (Sekisui Diagnostics, Burlington, MA), which is sensitive and specific and gives results in approximately 10 minutes. The rapid antigen test cannot be used in males. (11)(12)

How to Treat?

The CDC 2015 STD treatment guidelines recommend using metronidazole or tinidazole to treat *Trichomonas* vaginitis (Table 1). (3) If a patient does not respond to multiple regimens of these medications, swabs

Table 1. Treatment Guidelines for Vaginitis

TRICHOMONAS	BACTERIAL VAGINOSIS	*CANDIDA ALBICANS*
Treatment		
Metronidazole[a] 2 g orally once	Metronidazole 500 mg twice a day for 7 d	A. Over the counter
OR	OR	Clotrimazole 1% or 2% cream 5 g intravaginally daily for 7 or 3 d, respectively
Tinidazole[b] 2 g orally once	Metronidazole gel 0.75%, 2 g intravaginally at night for 5 d	OR
OR	OR	Miconazole 2% or 4% cream 5 g intravaginally daily for 7 or 3 d, respectively
Metronidazole 500 mg orally twice a day for 7 d	Clindamycin cream 2%, 2 g intravaginally at night for 7 d	OR
	OR	Miconazole 100-, 200-, or 1,200-mg vaginal suppository, one daily for 7, 3, or 1 d, respectively
	Clindamycin 300 mg orally twice a day for 7 d	OR
	OR	Tioconazole 6.5% ointment 5 g intravaginally as a single application
	Tinidazole 2 g orally for 2 d	B. Prescription
	OR	Butoconazole 2% cream, 5 g intravaginally as a single dose
	Tinidazole 1 g orally once a day for 5 d	OR
	OR	Terconazole 0.4% or 0.8% cream, 5 g intravaginally daily for 7 or 3 d, respectively.
	Secnidazole 2 g as a single dose (granules)	OR
		Terconazole 80 mg vaginal suppository, 1 daily for 3 d
		OR
		Fluconazole 150 mg orally in a single dose
Treatment for Resistant/Recurrent Disease		
Metronidazole 500 mg orally twice a day for 7 d (if 1-d treatment used before)	Repeat the same treatment	Initial:
OR	OR	7–10 d of a topical therapy OR
Metronidazole 2 g daily for 7 d	Metronidazole gel 0.75%, twice weekly for 4–6 mo	100-, 150-, or 200-mg oral dose of fluconazole every third day for a total of 3 doses
OR	OR	Followed by:
Tinidazole 2 g daily for 7 d	Metronidazole 500 mg orally twice per day for 1 wk followed by 600 mg of boric acid intravaginally for 3 wk followed by 0.75% metronidazole gel twice weekly for 4–6 mo	Oral fluconazole (100-, 150-, or 200-mg dose) weekly for 6 mo

[a]Patients should be advised to abstain from alcohol use during treatment with oral metronidazole and tinidazole and for 24 and 72 hours after the last dose of metronidazole and tinidazole, respectively.
[b]Tinidazole is contraindicated during pregnancy.
Modified from Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Diseases characterized by vaginal discharge: vulvovaginal candidiasis. *MMWR Recomm Rep.* 2015;64(No. RR-03):1–137.

should be sent to the CDC for culture and susceptibility testing.

Patients should be advised to abstain from sexual activity until both partners have been treated and are without symptoms. Testing for other STIs and HIV should also be performed. (3)

Management of Sex Partners

All patients who test positive and are treated should be counseled to communicate this diagnosis to their partner(s) and have their partner(s) seek comprehensive STI testing and treatment. Some states allow EPT: the provision of empirical treatment (antibiotics) and educational materials to partners. The CDC map for states that allow EPT is available in the CDC 2015 guidelines for the treatment of STIs (https://www.cdc.gov/std/ept/legal/default.htm).

Follow-up

Because patients often are infected again with *Trichomonas,* repeated testing 3 months after the initial treatment is recommended. (3)

Reporting

Trichomoniasis is not considered a reportable disease.

Prevention and Patient Counseling

Patients should be counseled about the following:

1. *Trichomonas* is an STI and most patients are asymptomatic.
2. Treatment is available and partners should also be treated. Abstinence should be practiced until both partners are treated and asymptomatic for at least 7 days.
3. Untreated *Trichomonas* infection in pregnancy increases the likelihood of complications of pregnancy, such as "preterm labor, premature rupture of membranes and low birth weight." (6)
4. Untreated *Trichomonas* infection also increases susceptibility to HIV acquisition.
5. Simultaneous consumption of metronidazole and alcohol may cause adverse effects, such as headaches, nausea, stomachaches, and flushing.
6. Risk reduction strategies include using condoms, abstinence, monogamous relationships, and limiting the number of sexual partners.

BACTERIAL VAGINOSIS

What Causes BV?

Although BV is not typically classified as an STI, it is often associated with sexual activity and is a common cause of vaginal discharge. BV is usually caused by an overgrowth of BV-associated bacteria. These are anaerobic bacteria that replace the normal flora (lactobacilli) of the vagina. These bacteria include *Gardnerella vaginalis, Atopobium vaginae, Mobiluncus curtisii, Mycoplasma hominis,* and *Ureaplasma* species. (13)

Epidemiology

BV has a prevalence of approximately 29% in women of reproductive age. (14) Although most women are asymptomatic, it is the most common diagnosis in women presenting with abnormal vaginal discharge. (13) Having new or multiple partners of either sex, not using condoms, douching, or factors that reduce vaginal lactobacilli can increase the risk of acquiring BV. (14)(15) Studies demonstrating that women usually develop BV only after they are sexually active, and other studies showing the similarity of vaginal bacterial flora in women in same-sex relationships, support the hypothesis that BV is often sexually transmitted. (16)

Women with BV are predisposed to infection with other STIs. Recurrence of BV is common, and treating male sex partners does not prevent recurrence. (17)

Signs and Symptoms

Most women with BV are asymptomatic. Approximately 50% of women with BV present with a white, homogenous discharge that has a fishy odor. The foul odor often increases after sexual intercourse or at the end of a menstrual cycle.

When to Test?

There are no guidelines to recommend testing in asymptomatic patients. In patients presenting with an abnormal discharge, specific clinical criteria with laboratory testing may be used to make the diagnosis.

1. Amsel diagnostic criteria (18): The diagnosis of BV using the Amsel criteria requires 3 of the following 4 symptoms or signs: homogeneous, thin, white discharge; presence of clue cells (vaginal epithelial cells covered with bacteria so that the cell walls are not visible) on microscopic examination of a normal saline slide of vaginal secretions (20% of cells in high power must be clue cells) (Fig 3); pH of vaginal fluid greater than 4.5; and presence of a fishy odor that develops after discharge contact with 10% KOH ("the whiff test").
2. Gram-stain: This is considered the gold standard for diagnosing BV. The Nugent score is a scoring system that helps determine the proportion of lactobacilli to bacteria associated with BV. The score ranges from 1 to 10, and BV is diagnosed if the score is between 7 and 10 (indicating a greater proportion of BV-associated bacteria compared with normal flora). Using the Nugent scoring system as the gold standard, the Amsel criteria were found to have sensitivity, specificity, and positive and negative predictive

values of 78.72%, 92.35%, 75.51%, and 93.54%, respectively. (19)

3. Other tests include the recently approved polymerase chain reaction test BD MAX™ vaginal panel test (BD, Franklin Lakes, NJ), which detects different causes of vaginitis. This has sensitivity and specificity of 89.8% and 96.5%, respectively, for the detection of BV. (20) Culture and Papanicolaou smear have very low sensitivity and specificity and are not recommended. Indirect tests that detect enzymatic activity of the bacteria are also available. (21)(22)

How to Treat?

Treatment is recommended for symptomatic women with BV. The CDC recommends treatment with metronidazole, tinidazole, or clindamycin. Various regimens are available for the treatment of primary and recurrent infections (Table 1). (3) HIV infection does not change the management of BV.

What's New?

Secnidazole (2 g as a single dose) was approved in September 2017 for the treatment of BV. Secnidazole is available as granules that are sprinkled on food and must not be chewed, crushed, or broken when swallowing. Food should be consumed soon after being treated with secnidazole (within 30 minutes). (23)

Management of Sex Partners

Male sexual partners do not need to be treated, but same-sex female partners should be offered testing and treatment. (3)

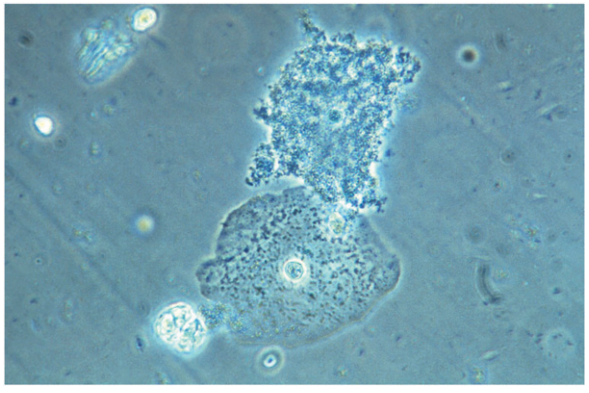


Figure 3. Photomicrograph of a vaginal smear specimen depicts 2 epithelial cells: a normal cell and an epithelial cell with its exterior covered by bacteria, giving the cell a roughened, stippled appearance known as a clue cell. These are typically seen in bacterial vaginosis. (Reprinted with permission from the Centers for Disease Control and Prevention's Public Health Image Library. Source of original image: M. Rein, 1978.)

Follow-up

Follow-up is not routinely recommended if the patient's symptoms resolve. However, recurrences occur in approximately 50% of women within a year.

Recurrent BV. For multiple recurrences the same treatment may be offered or other regimens are recommended (Table 1). (24)(25)

Reporting

BV is not considered a reportable disease.

Prevention and Patient Counseling

Patients should be counseled about the following:

1. Women with BV often do not have symptoms; routine screening is not recommended. Typical symptoms include a foul-smelling vaginal discharge.
2. BV is caused by an overgrowth of vaginal bacteria and an associated reduction in lactobacilli.
3. Symptoms of BV usually start after the onset of sexual activity, and BV may be transmitted between women in same-sex relationships.
4. BV infection may increase the chance of acquiring other STIs, including HIV, and women who have both HIV and BV may be more likely to transmit HIV to their male partners.
5. BV has been associated with premature deliveries in pregnant women and with PID.

VULVOVAGINAL CANDIDIASIS

What Causes VVC?

VVC is most commonly caused by *Candida albicans*. It is not an STI but can cause clinical symptoms similar to some STIs. The vagina is home to different *Candida* species that constitute a normal part of the vaginal flora. However, with disruption of the vaginal milieu, yeast overgrowth can cause symptomatic vaginitis. (26) Prepubertal girls are not usually affected by candidiasis because the vaginal lining is thin and the pH is alkaline.

Epidemiology

According to the CDC, approximately 75% of women will "have at least one episode of VVC, and 40-45% will have two or more episodes." (3) "Recurrent vulvovaginal candidiasis, defined as a minimum of four episodes per year, occurs in about 5% to 10% of the female population." (26)(27)

Women who are diabetic, taking repeated courses of antibiotics or corticosteroids, on hormone replacement therapy, on oral contraceptives, or have an intrauterine device (IUD) are predisposed to recurrent VVC. Pregnancy, spermicide and condom use, and HIV infection are also risk factors for recurrent disease. (26)(27)

Signs and Symptoms

VVC often presents with itching, burning with urination, vaginal discharge, and painful sexual activity. (3) The infection is characterized by a white, clumpy, "cottage cheese"-like discharge. Symptoms may increase before menstruation. VVC may be categorized as uncomplicated or complicated. (3)

Uncomplicated VVC is usually not as severe, occurs less frequently (<4 times per year), and usually has *C albicans* as the etiologic agent. Uncomplicated VVC often occurs in women who are immunocompetent and not pregnant and respond to all first-line treatments.

Complicated VVC is usually recurrent or severe, often occurring in pregnant women or those who are immunocompromised, diabetic, or debilitated. Complicated VVC is often due to non-*albicans Candida* species. Vaginal candidiasis occurring more than 4 times per year in immunocompetent women is also treated as complicated VVC.

When to Test?

Patients presenting with complaints of abnormal vaginal discharge, pruritis, or vulvar irritation should undergo diagnostic evaluation.

How to Test?

The following tests for candida can be used:

1. Vaginal pH: usually normal (<4.5).
2. Wet mount: Visualization under a microscope of budding yeast and/or pseudohyphae can confirm the diagnosis of VVC. A 10% KOH preparation has higher sensitivity for detection of yeast compared with a saline wet mount because KOH breaks down other cellular material (Fig 4). (27)
3. Culture: If the wet mount is negative in a symptomatic patient, fungal cultures may be performed. A positive culture in an asymptomatic patient may reflect colonization and is not an indication for treatment. Non-*albicans* disease is often identified by culture. Fungal culture should be performed before starting suppressive therapy for recurrent VVC. (28)

Polymerase chain reaction testing for yeast has not been FDA approved.

How to Treat?

The CDC 2015 STD treatment guidelines recommend azoles, over-the-counter and by prescription, for the treatment of uncomplicated VVC (Table 1). (3)

For recurrent VVC (4 episodes per year), a longer initial course of therapy (7–14 days) followed by maintenance treatment for 6 months is recommended (Table 1). (3) Symptoms return in approximately 30% to 50% of women once maintenance therapy is discontinued. (3)

For severe VVC with extensive skin breakdown, edema, and fissure formation, prolonged treatment is recommended (Table 1). (3)

Treatment of Non-*Albicans* VVC

The preferred treatment for non-*albicans* VVC has not been identified. Use of a nonfluconazole azole for prolonged periods in the oral or topical form is recommended as initial therapy. If symptoms do not resolve with this regimen then alternative treatment with 600 mg of boric acid encapsulated in gelatin (Hylafem®; US Pharmaceutical Corp, Decatur, GA) intravaginally once daily for 2 weeks may be tried. (25)(29)

Management of Partners

No treatment is required for asymptomatic sexual partners of infected women. VVC is not sexually transmitted, although male partners can occasionally develop candida balanitis.

Follow-up

No specific follow-up is recommended after treatment of uncomplicated VVC. If symptoms return, women should return for further evaluation.

Prevention and Patient Counseling

Patients should be counseled about the following:

1. Colonization by *Candida* is common; if asymptomatic, treatment is not necessary.
2. VVC is not sexually transmitted. Rarely, male partners can develop candida balanitis.

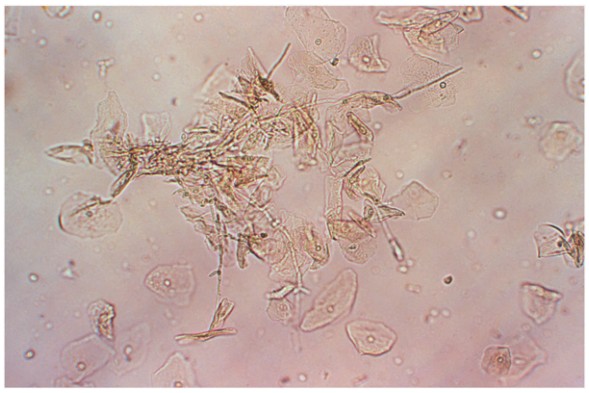


Figure 4. Photomicrograph of a wet-mounted vaginal smear specimen extracted from a patient with vaginal candidiasis reveals the presence of *Candida albicans* (with blastopores and pseudohyphae). (Reprinted with permission from the Centers for Disease Control and Prevention's Public Health Image Library. Source of original image: Dr Stuart Brown, 1976.)

3. Symptomatic *Candida* infection is usually triggered by disturbance of the normal vaginal environment.
4. Patients should be advised to avoid repeated self-treatment of persistent abnormal vaginal discharge with over-the-counter topical antifungals or taking unnecessary antibiotics. Douching should also be avoided.

CHLAMYDIA

What Causes Chlamydial Infections?

Chlamydia trachomatis is an obligate intracellular bacterium that resembles gram-negative organisms.

Epidemiology

C trachomatis is the "most prevalent bacterial sexually transmitted infection" in the world, and the most frequently reported STI in the United States, with "more than 1.5 million cases reported in 2016." (2)(30) Rates of reported cases are highest among adolescents and young adult women aged 15 to 24 years. Having multiple sexual partners, using oral contraceptive pills, having another STI, and lack of condom use also increase the risk of acquiring a chlamydial infection. (31) Overall prevalence in women aged 15 to 24 years was 4.7%. (32)

Signs and Symptoms

Most infected men and women are either asymptomatic or minimally symptomatic.

Men: If symptomatic, men develop urethritis with or without discharge, which can be mucoid, clear, or mucopurulent, known as "nongonococcal urethritis." Epididymitis may occur presenting with unilateral scrotal pain, edema, and tenderness, with or without a urethral discharge.

Women: If symptomatic, women may present with cervicitis causing abnormal vaginal discharge. Symptoms are usually nonspecific, such as irregular bleeding or pelvic discomfort. Signs of infection include friability of the cervix (bleeding on touching the cervix) and mucopurulent cervical discharge. Urethral involvement will cause dysuria and frequency of urination.

Untreated chlamydial infections can result in complications, including PID, ectopic pregnancy, and infertility. (33) Women presenting with right upper quadrant pain, nausea and vomiting, and signs of PID on physical examination may have Fitz-Hugh-Curtis syndrome or perihepatitis as a complication of chlamydia.

Both sexes may present with conjunctivitis (due to autoinoculation), severe pharyngitis (genital-oral contact), proctocolitis or proctitis (receptive anal intercourse), or reactive arthritis (as a complication of chlamydial infection).

When to Test?

Asymptomatic: Per the CDC 2015 screening guidelines (3):

1. Annual screening of all sexually active women younger than 25 years is recommended (this should be included as a routine part of an annual examination for adolescents and young adults), including women who have sex with women. (3)(31)
2. Routine screening of sexually active young men is not mandatory; annual screening is recommended in those presenting to clinical settings with a high prevalence of patients with chlamydia, such as adolescent and STD clinics, and in MSM, in whom testing should be performed from both genital and rectal sites. (31)
3. Screening of transgender individuals should be based on "age, sexual practices and current anatomy." (3)
4. In pregnant women younger than 25 years, screening should be performed in the first and third trimesters. If testing positive, these women should be treated and tested again at 4 weeks for a test of cure and again 3 months after treatment. (3)
5. HIV-positive individuals (who are sexually active) should be tested at the first visit and then every year. (3)

Symptomatic: Infections are usually asymptomatic, which is why screening is so important, but testing for chlamydia should always be performed in a sexually active patient presenting with vaginal discharge or urethritis.

How to Test?

NAATs are considered the gold standard for diagnosis of chlamydia in both men and women. These tests are approved for first-catch urine in men and women, vaginal or endocervical swabs in women, and urethral swabs in men. (3) Results from vaginal swabs are better than those from NAATs performed on urine; patient-obtained swabs are well-accepted by women of all ages and are at least equivalent and sometimes perform better than those obtained by providers. (34)

Oropharyngeal or rectal chlamydia can be diagnosed using NAATs (although this testing approach is not FDA approved), which are thought to be more sensitive than culture. Rectal swabs may also be patient collected, and results have been shown to be comparable with those collected by providers. (3)(34)

Cell culture has lower sensitivity than NAAT and is limited to specimens obtained during evaluations of children for possible sexual assault.

Table 2. Treatment Guidelines for Pelvic Inflammatory Disease

Outpatient treatment	Ceftriaxone 250 mg IM (single dose) OR Cefoxitin 2 g IM (single dose) + probenecid 1 g orally (given concurrently) PLUS Doxycycline 100 mg orally twice per day/14 d PLUS Metronidazole 500 mg orally twice per day/14 d[a]
Inpatient or parenteral therapy	1. Regimen 1 Cefotetan 2 g IV every 12 h OR cefoxitin 2 g IV every 6 h PLUS Doxycycline 100 mg orally or IV every 12 h/14 d[bc] 2. Regimen 2 Clindamycin 900 mg IV every 8 h PLUS Gentamycin 2 mg/kg IV or IM (loading dose) followed by 1.5 mg/kg every 8 h (can switch to daily dosing of 3–5 mg/kg IV) (Oral therapy with clindamycin 450 mg orally 4 times per day or doxycycline 100 mg orally twice per day can be used to complete the 14 d of treatment.)[c] 3. Regimen 3 Ampicillin sulbactam 3 g IV every 6 h PLUS Doxycycline 100 mg orally or IV every 12 h/14 d[c]
Alternative treatment	1. Regimen 1 Azithromycin 500 mg IV daily for 1–2 doses followed by 250 mg orally daily for 12–14 d +/– Metronidazole 500 mg orally twice daily 2. Regimen 2 Ceftriaxone 250 mg IM (single dose) PLUS Azithromycin 1 g weekly/2 wk OR doxycycline 100 mg orally twice daily/14 d 3. Regimen 3 Levofloxacin 500 mg orally once daily OR ofloxacin 400 mg orally twice daily OR moxifloxacin 400 mg orally once daily[d] PLUS Metronidazole 500 mg orally twice daily

IM=intramuscular; IV=intravenous.

[a]Because ceftriaxone has limited coverage of anaerobes, metronidazole use should be considered in conjunction with it and other third-generation cephalosporins until it is established that extended anaerobic coverage is not important in the treatment of pelvic inflammatory disease.

[b]Oral therapy with doxycycline should be started 24 to 48 hours after clinical improvement is noted and should be considered at all times because intravenous doxycycline is painful.

[c]If a tubo-ovarian abscess is present then clindamycin 450 mg orally 4 times per day or metronidazole 500 mg orally twice per day should be added to complete the 14 days of therapy with doxycycline.

[d]The Centers for Disease Control and Prevention does not recommend fluoroquinolone-containing regimens for routine treatment of pelvic inflammatory disease. If a fluoroquinolone is used then testing for gonorrhea should be performed and if positive then susceptibilities must be obtained.

Modified from Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Pelvic inflammatory disease (PID). *MMWR Recomm Rep.* 2015;64(No. RR-03):1–137.

How to Treat?

All chlamydia-positive individuals should be treated as soon as possible to prevent reproductive health complications. (35) Recommended treatment regimens (CDC 2015) (3) for urogenital infection and oropharyngeal infection are as follows:

Treatment is with azithromycin 1 g as a single dose or doxycycline 100 mg orally taken twice per day for 7 days. To improve adherence, directly observed treatment with single-dose azithromycin is preferred. (3)

Other treatments include erythromycin base 500 mg or erythromycin ethylsuccinate 800 mg 4 times per day, or levofloxacin 500 mg daily or ofloxacin 300 mg orally twice per day for 7 days. (3) Abstinence should be practiced for 7 days after treatment is complete and after sexual partners have been treated. Testing for other STIs, including HIV, should be offered to patients diagnosed as having chlamydia.

In pregnant women, azithromycin 1 g orally as a single dose or alternate treatment with amoxicillin or erythromycin

base can be used. Doxycycline and erythromycin estolate are contraindicated in pregnant women.

Management of Sex Partners

Sex partners should get tested and empirically treated. In patients with urogenital infections, the CDC recommends that "all partners that the patient has had sexual relations with in the past 60 days and the most recent partner even if more than 60 days should be referred for testing and treatment." (3) EPT should be considered for partners as permitted by state laws because this has been shown to reduce the rates of recurrence or the persistence of chlamydial infection. (36)

Follow-up

Test of cure is the term used to retest infected patients to assess for resolution of the initial infection. Although performing a test of cure is no longer recommended (except in pregnant women), repeated testing is recommended for all chlamydia-infected individuals 3 months after treatment to assess for repeated infection. (37)(38) A test of cure, if performed, should not be undertaken earlier than 3 weeks after treatment.

Prevention and Patient Counseling

The patient should be counseled about 1) the importance of routine screening for chlamydia to prevent reproductive health complications (especially in young women), 2) the asymptomatic nature of most chlamydial infections, 3) the importance of treatment of partners and the high rate of repeated infection, 4) the need to abstain from unprotected sexual intercourse after treatment for at least 7 days, and 5) risk reduction strategies (as detailed in previous sections).

GONORRHEA

What Causes Gonorrhea?

Gonorrhea is caused by a gram-negative diplococcus (*Neisseria gonorrhoeae*) transmitted sexually by penile-vaginal intercourse, oral-genital contact, and anal intercourse and perinatally at the time of vaginal delivery.

Epidemiology

After chlamydia, gonorrhea is the most commonly reported STI, with approximately 820,000 new infections in the United States each year. (1) The highest rates of gonorrhea are found in men aged 20 to 24 years, in the southern states, and in African Americans and Native Americans. A history of gonorrhea or other STIs increases the risk of a new infection. Other risk factors include having new sex partners and engaging in commercial sex. (2)

The rate of gonorrhea has been increasing steadily since 2009 from 98.1 cases per 100,000 to 145.8 cases per 100,000 population in 2016. (2)

Signs and Symptoms

The incubation period is 1 to 14 days.

Men: Most men are symptomatic, presenting with symptoms of urethritis, ie, with a mucopurulent or purulent urethral discharge and dysuria. Men engaging in anal sex may also present with signs and symptoms of proctitis, including anal bleeding, itching, irritation, painful defecation, or a painless purulent anal discharge. Complications in men may include epididymitis, prostatitis, and perirectal or periurethral abscess.

Women: Gonorrhea is often asymptomatic in women but may present with cervicitis or urethritis. Complications in women include infection or unilateral abscesses in the accessory glands, such as the Skene glands or Bartholin glands, PID, or perihepatitis.

Men and women: Ocular infections, pharyngeal infections, and disseminated infections can occur in both sexes. Disseminated gonococcal infections are more common in women and those who have complement deficiency. Usually associated with bacteremia, disseminated gonococcal infection presents as a multisystem disorder that may involve the skin, joints and tendons, heart, liver, and, occasionally, meninges.

When to Test?

Asymptomatic: Per the CDC 2015 screening guidelines, (3) annual screening is recommended for all sexually active women younger than 25 years. In addition, screening is recommended for men and older women at increased risk for infection, including those with new partners or partners with an STI, and for MSM.

Symptomatic: Most gonorrhea infections are asymptomatic in women but typically cause urethritis symptoms in men, prompting an evaluation. (3)

How to Test?

1. NAAT: The preferred testing method is NAAT of endocervical, vaginal, and urethral swabs or urine. NAATs are most sensitive but are not FDA cleared for rectal or oropharyngeal specimens, although some laboratories are able to perform these tests with a Clinical Laboratory Improvement Amendments waiver.
2. Gram-stain: In symptomatic males, a Gram-stain demonstrating leukocytes and gram-negative diplococci from

a urethral specimen can be diagnostic with very high sensitivity (>95%) and specificity (>99%). A Gram-stain is not recommended in asymptomatic males. (39)

3. Culture: Culture is not as sensitive as NAAT but it has the advantage of being approved for use at extragenital sites (rectal, oropharyngeal, and conjunctival) and for checking microbial susceptibility.

How to Treat?

The CDC 2015 recommended guidelines for gonorrhea include the following:

1. Uncomplicated gonorrheal infections of the cervix, urethra, and rectum:
   Ceftriaxone 250 mg intramuscularly (IM) in a single dose along with azithromycin 1 g orally in a single dose OR
   Cefixime 400 mg orally with azithromycin 1 g orally in a single dose. (This should be considered only if IM ceftriaxone is not available because there is increasing resistance of gonococci to cefixime.) (3)
2. Gonorrheal pharyngeal infections:
   Ceftriaxone 250 mg IM in a single dose along with azithromycin 1 g orally. The alternative regimen (including cefixime) is not as effective. If alternative regimens are used. then a test of cure must be performed 14 days after treatment with NAAT and culture. If NAAT results are positive, then a culture with antimicrobial sensitivities should be performed before repeated treatment. (3)
3. Gonococcal conjunctivitis:
   Ceftriaxone 1 g IM with azithromycin 1 g orally in a single dose. Lavaging the eye with normal saline is also recommended. (3)
4. Disseminated gonococcal infection:

This infection requires hospital admission of the patient and consultation with infectious disease specialists because disseminated disease can have serious complications. Parenteral therapy is indicated and consists of ceftriaxone 1 to 2 g intravenously (IV) every 12 to 24 hours for at least 7 days with azithromycin 1 g orally in a single dose. If disseminated gonococcal infection is complicated by meningitis or endocarditis, then parenteral therapy should continue for 2 or 4 weeks, respectively. (3)

What's New?

Gonorrhea has developed increasing resistance to certain antimicrobial agents. (40) Therefore, combination therapy with 2 antimicrobial drugs is recommended even if patients are not co-infected with chlamydia. Oral cefixime is no longer recommended as an equivalent alternative to IM ceftriaxone but can be considered only if IM ceftriaxone is not available. (3)

For individuals who are severely allergic to cephalosporins, alternative treatments have shown efficacy in urogenital gonorrhea, including combining 2 g of oral azithromycin with either gentamycin 240 mg IM or gemifloxacin 320 mg orally. (41)

Management of Sex Partners

All sexual partners of the patient (from the past 60 days) should seek evaluation, laboratory testing, and empirical treatment using 2 drugs as recommended. The most recent sexual partner should be treated no matter when the sexual contact occurred (ie, even if >60 days). (3) EPT can be provided to heterosexual male and female partners. EPT consists of cefixime 400 mg with azithromycin 1 g orally in a single dose. (36)

EPT should not be considered if 1) a female partner is experiencing symptoms of PID (because that warrants a complete evaluation by a clinician) or 2) MSM due to the high risk of co-infection with syphilis or HIV, lack of efficacy data, and increasing resistance to cefixime in gonococcal strains isolated from this population.

Abstinence from unprotected sexual contact should be recommended for 7 days after both the patient and the partner have been treated and all symptoms have resolved so that repeated infection can be prevented. (3)

Follow-up

A test of cure is recommended only for patients who have pharyngeal gonorrhea and have been treated with an alternative regimen. A test of cure is not indicated in those treated for uncomplicated urogenital or rectal gonorrhea with traditional regimens. (3) If symptoms persist after recommended treatment regimens then a culture should be performed (with or without NAAT) and antimicrobial susceptibility should be checked on any isolate. Patients should be tested again from the original anatomical site of infection 3 months after treatment because repeated infection is common due to exposure to an infected partner. (3) Patients with persistent symptoms or repeated NAAT-positive results who deny the possibility of repeated infection should also have a culture with sensitivities performed.

Prevention and Patient Counseling

The patient should be counseled about

1. The importance of routine screening for gonorrhea to prevent reproductive health complications of untreated infections, especially in young women.
2. The asymptomatic nature of most gonococcal infections in females, whereas males often present with symptoms.
3. The importance of treating partners and the high risk of repeated infection.

4. The need to abstain from intercourse after completion of treatment for both partners for at least 7 days and while symptomatic.
5. Risk reduction strategies, including consistent condom use, should also be emphasized.

CASE (VERSION 2)

The same 17-year-old girl presents to the clinic with increased foul-smelling vaginal discharge but this time also reports lower abdominal pain and chills.

On Examination

The patient's temperature is 100.6°F (38.1°C), blood pressure is 105/65 mm Hg, and heart rate is 76 beats/min. She has lower abdominal tenderness but no rebound or guarding. On speculum examination a purulent discharge is seen in the vagina. She is uncomfortable and reports pain with movement of the cervix and left adnexal tenderness. There is no palpable adnexal fullness or mass.

Vaginal swab specimens are sent to test for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis*. A urine pregnancy test is negative. Wet prep slides reveal many white blood cells but only a few clue cells and no trichomonads.

Diagnosis

Pelvic inflammatory disease.

Treatment

The patient is treated in the office with ceftriaxone 250 mg IM and prescribed oral doxycycline 100 mg twice a day for 14 days. Syphilis and HIV testing are also performed, and she is advised to notify her partner to obtain testing and empirical treatment for gonorrhea and chlamydia.

Later that day she vomits immediately after taking the doxycycline. She is admitted to the hospital for short-term management with IV antibiotics. She responds well after 48 hours and is discharged to complete the oral course of doxycycline. She is seen in the clinic 3 days later for close follow-up and additional risk reduction counseling.

PELVIC INFLAMMATORY DISEASE

PID is usually a consequence of infection by chlamydia or gonorrhea in the upper female genital tract. PID results from infection and inflammation of different parts of the female reproductive system, including the uterus, fallopian tubes, and ovaries. In most cases PID is caused by an ascending infection from the cervix and vagina. PID may be an acute syndrome (symptoms present for <30 days) or a subclinical or chronic syndrome (symptoms present for 30 days).

What Causes PID?

Most commonly, acute PID is caused by *C trachomatis* and *N gonorrhoeae*. However, other organisms, including aerobic gram-negative rods such as *Escherichia coli*, anaerobes such as *Bacteroides*, gram-positive organisms such as *Streptococcus*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and in some women bacteria related to BV, have all been implicated. (42) The etiologic agents in chronic PID are often *Mycobacterium tuberculosis* or *Actinomyces* species. (42)

Epidemiology

The incidence of PID is difficult to determine because it is not a reportable disease, and many women may have minimal symptoms. Using self-reported data in sexually active women 18 to 44 years old, the NHANES data determined that approximately 2.5 million females have had PID in their lifetime. (43) Although the incidence of chlamydia is increasing, the CDC data show a decline in the incidence of PID by approximately 70% from 2005 to 2014. (2) This is attributed to the increase in chlamydia screening, resulting in early detection, treatment, and reduction of ascending infection, which causes PID. (44)

Risk factors for developing PID are similar to those for acquiring the STIs that often cause PID, including younger age (<20 years old), having multiple sexual partners, having chlamydia or gonorrhea or having a partner with these infections, vaginal douching, using oral contraceptive pills, or recent insertion of an IUD. The risk of PID increases 6-fold in the first 3 weeks after insertion of an IUD, although it returns to the baseline risk after that period. Vaginal douching causes alteration of the vaginal flora, disruption of the vaginal epithelium and the mucosal barrier of the cervix, thus predisposing to PID. (45)(46)(47)

Signs and Symptoms

Women with PID can be asymptomatic or can present with acute, subacute, or chronic symptoms. Acute PID is diagnosed when symptoms are present for 30 days or less. Patients may present with "mild" nonspecific symptoms such as dyspareunia, dysuria, or abdominal pain; moderate PID usually has more specific symptoms, such as pelvic or lower abdominal pain or cramping, bleeding after sexual activity, painful urination, and vaginal discharge and is often associated with specific signs of PID, including cervical motion and uterine or adnexal tenderness. Systemic signs and symptoms are usually present in women with severe PID and include fever, chills, purulent or mucopurulent vaginal

discharge, and gastrointestinal symptoms such as nausea and/or vomiting. Signs are similar to those seen with moderate disease. Associated laboratory findings may include an elevated white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level. (42)(48) Acute complications include salpingitis, tubo-ovarian abscess, and perihepatitis. Chronic complications include ectopic pregnancy, infertility, and chronic pelvic pain. The chances of infertility are 8%, 20%, and 50% after 1, 2, and 3 episodes of PID, respectively. Women who have had PID are 6 times more likely to have an ectopic pregnancy. (42)(49)(50)

How to Test/Diagnose?

Providers should have a low threshold for diagnosing and treating PID because untreated PID can have serious long-term complications for young women. Symptoms of acute PID can mimic many other diseases, and there are no specific symptoms, signs, or laboratory tests that can accurately diagnose this condition. (51) Laparoscopy could possibly confirm the etiologic agent; however, this is not easily available to most providers and may delay early treatment of the condition. Most often treatment is started after a clinical diagnosis with sensitivity of 65% to 90%. (3)(52)(53)(54)(55)

The CDC 2015 STD treatment guidelines (3) recommend that treatment for PID should be started empirically in sexually active young women or others at risk for STIs presenting with pelvic or abdominal pain (in whom no other cause other than PID can be identified) if they have even 1 of the following clinical findings: uterine tenderness, cervical motion tenderness, or adnexal tenderness.

One or more of the following additional criteria can help increase the specificity of the clinical diagnosis of PID: 1) elevated oral temperature greater than 101°F (38.3°C), 2) elevated erythrocyte sedimentation rate, 3) elevated C-reactive protein level, 4) presence of mucopurulent vaginal discharge or cervical friability, 5) increased white cells on saline smear of vaginal fluid, and 6) positive cervical testing for chlamydia or gonorrhea (3)

Definitive diagnosis can be made by endometrial biopsy showing pathologic evidence of endometritis by ultrasonography or other imaging techniques to show fluid-filled tubes or tubo-ovarian complex or tubular hyperemia visible on Doppler, or by laparoscopy showing evidence of PID. (48)

How to Treat?

Prompt diagnosis and early treatment are essential to prevent complications. Delay in treatment by as little as 3 days can result in increased chances of infertility and ectopic pregnancy. (56)

When should one hospitalize the patient with PID? Acute PID may require hospitalization particularly in adolescent patients.

Criteria for hospitalization include 1) inability to confirm the diagnosis and exclude other conditions that may require surgery, such as acute appendicitis; 2) presence of a tubo-ovarian abscess; 3) severe illness with systemic symptoms; 4) pregnancy; 5) HIV infection; and 6) failure to respond to outpatient oral treatment (within 48–72 hours) or inability to tolerate the oral treatment.

Some adolescent patients who cannot be relied on to comply with medications or do not have a support system may need to be hospitalized as well. (3)(48)

Given the need to start treatment early and empirically, broad spectrum antibiotics that provide coverage for both chlamydia and gonorrhea and other possible pathogens are used.

In acute severe PID (especially if patients are hospitalized), parenteral (IV) therapy with cephalosporins and doxycycline is used initially, followed by oral therapy within 48 to 72 hours if a clinical response to treatment is evident. Oral therapy must be continued for 14 days (Table 2). (3)

In mild-moderate disease, oral/IM regimens with similar antibiotics may be used in an outpatient or inpatient setting (Table 2). Outpatients receiving oral therapy must follow up at 72 hours for a repeated evaluation. If they do not show an improvement in symptoms, then hospitalization with a switch to parenteral therapy may be indicated. Oral metronidazole should be considered, especially if anaerobic organisms are suspected. (3)

The CDC recommends alternative regimens for individuals with cephalosporin allergies but does not recommend routine treatment with fluoroquinolones because of increasing resistance of *N gonorrhea* to this group of antibiotics unless sensitivities are obtained (Table 2). (3)

If a tubo-ovarian abscess is suspected then the patient should be hospitalized and started on broad spectrum IV antibiotics that provide coverage for gram-negative, gram-positive, and anaerobic organisms (Table 2). Pelvic ultrasonography should be performed, and the patient should be hospitalized for initial management. Surgical consultation should be considered if the patient does not show clinical improvement or if imaging indicates persistence of the abscess. (3)(57)

Management of Sex Partners

All male sex partners in the past 60 days should seek evaluation, undergo laboratory testing, and be treated empirically for both chlamydia and gonorrhea. The last sexual partner should be treated even if the contact was more than 60 days ago. EPT can be provided to partners of women with PID. (3)

Follow-up

All patients diagnosed as having PID should be seen and examined again within 3 days of treatment initiation. If patients do not demonstrate improvement in symptoms and signs of PID, such as reduction in fever or resolution or reduction of abdominal/pelvic pain, cervical motion, or adnexal or uterine

tenderness, then they should be hospitalized and treated according to the CDC guidelines. Follow-up of all women who are chlamydia or gonorrhea positive at 3 to 6 months is recommended because the chances of repeated infection are high. (3)

Prevention and Patient Counseling

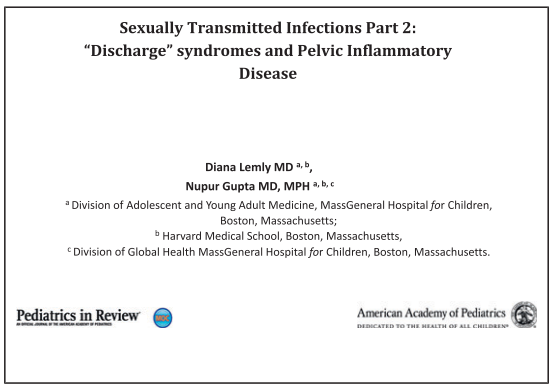
Patients should be counseled that

1. Women with PID can present with acute symptoms related to the reproductive tract or vague, nonspecific symptoms, or they may be asymptomatic.
2. Recurrent PID may present with different types of symptoms. (42)(48)
3. PID has many etiologic agents but the most common are *C trachomatis* and *N gonorrhoeae* transmitted from males to females by unprotected sexual intercourse.
4. Abstinence from intercourse for at least 7 days after completion of treatment and resolution of symptoms for both partners is recommended. (3)
5. Delay in treatment or untreated PID can lead to chronic pelvic pain, infertility, or ectopic pregnancy. (56)
6. Women who have had PID are at increased risk for future episodes of the disease. (42)(48)
7. Risk reduction strategies should be emphasized.

Summary

- Sexually transmitted infections disproportionately affect young people, with more than half of the infections occurring in youth aged 15 to 25 years. (1)(2)
- Based on some research evidence as well as consensus (strong recommendation, Level B all sexually active adolescent and adult females presenting with vaginal discharge should be tested for trichomoniasis, chlamydia, and gonorrhea. Bacterial vaginosis and vulvovaginal candidiasis should also be considered during the evaluation. (3)
- Based on research evidence (strong recommendation, Level B), the Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) recommend screening for chlamydia and gonorrhea in sexually active women 24 years and younger. (2)(3)(31) Based on strong research evidence (strong recommendation, Level A), nucleic acid amplification tests are the most sensitive and specific tests available for trichomonas, chlamydia, and gonorrhea and can be performed on provider- or patient-collected vaginal swabs in women and on urine in men and women. (3)(9)(58)(59)
- Based on Level B and C recommendations, patients should be retested for chlamydia and gonorrhea 3 months after treatment due to the high risk of repeated infection. (37)(38)
- As per CDC and USPSTF guidelines and Level A recommendation, all people aged 13 to 64 years should be screened for HIV, including all patients who seek evaluation or treatment for sexually transmitted diseases. (60)
- Based on strong research evidence (strong recommendation, Level A, Level B), the CDC 2015 sexually transmitted diseases guidelines include multiple effective treatment regimens for chlamydia, gonorrhea, trichomoniasis, bacterial vaginosis, vulvovaginal candidiasis, and pelvic inflammatory disease (PID). (3)
- Based on Level B recommendation, providers should have a low threshold for diagnosing and treating PID because untreated PID can have serious long-term complications for young women, as shown in large cohort studies. (3)(53)(56)
- Based on expert consensus (Level B, Level D), indications for hospitalization for PID include presence of a tubo-ovarian abscess, severe illness with systemic symptoms, pregnancy, human immunodeficiency virus infection, and failure to respond to outpatient oral treatment (within 48–72 hours) or inability to tolerate the oral treatment. (3)

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/41/No. 10/522.**



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1. A 17-year-old girl presents with vaginal discharge, dysuria, and vulvar discomfort. She has used an over-the-counter vaginal cream for 3 days with no improvement. Two months ago her male sexual partner tested positive for gonorrhea. They both received treatment and abstained from sexual activity for 7 days after treatment. Her sexually transmitted infection (STI) testing for gonorrhea, chlamydia, human immunodeficiency virus, and syphilis subsequently was negative for all. Their use of condoms has been inconsistent. Her last menstrual period was 3 weeks ago, and a urine pregnancy test today is negative. Examination of her genitalia discloses a copious green frothy discharge that has pH 6.5. There is a foul odor and labial irritation. There is no cervical motion tenderness or adnexal pain on bimanual examination. Vaginal swabs for wet mount preparations and nucleic acid amplification testing (NAAT) are obtained, and empirical treatment is initiated. Based on the clinical presentation, which one of the following is the most likely cause of this patient's vaginal discharge?

   A. Candidiasis.
   B. Chlamydia.
   C. Gonorrhea.
   D. Group B streptococcus.
   E. Trichomoniasis.

2. A 16-year-old girl tested positive for chlamydia on a routine annual screen for chlamydia and gonorrhea. She and her male partner of the past 6 months have no history of STIs and are both asymptomatic. He has had no male partners. During the past year she has had an "on and off" sexual relationship with a female partner. The patient is treated today with azithromycin 1 g orally as a single dose. Which one of the following is the most appropriate additional recommendation to give at this visit?

   A. All her sexual partners in the past 60 days should have STI testing and receive empirical treatment for chlamydia.
   B. Her sexual partners should not be provided expedited partner treatment.
   C. Only her current male partner needs STI testing and empirical treatment for chlamydia.
   D. The patient should be tested again for recurrent infection 6 and 12 months after treatment.
   E. The patient should have a test of cure 2 weeks after treatment.

3. A 17-year-old boy who has had 2 male sexual partners during the past year has engaged in receptive and insertive oral intercourse. He and his partners have no history of STIs. He has no symptoms suggestive of an STI, including no dysuria, urethral discharge, pharyngitis, or mouth lesions. NAAT for chlamydia and gonorrhea and serologic testing for human immunodeficiency virus and syphilis were performed. The results of the urine NAATs and serologic tests are negative. The oropharyngeal swab is positive for gonorrhea. The patient has no known drug allergies. Which one of the following is the next best step in the management of this patient?

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A. Azithromycin 2 g orally as a single dose.
B. Cefixime 400 mg orally as a single dose.
C. Ceftriaxone 250 mg intramuscularly.
D. Ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally as a single dose.
E. Levofloxacin 500 mg orally once daily for 14 days.

4. A 16-year-old girl presents to the clinic with vaginal discharge and intermittent vaginal spotting for 2 weeks. Her last office visit was 4 months ago when she was prescribed oral contraceptive pills. At that visit results of urine NAAT for chlamydia and gonorrhea were negative. Her last menstrual period was 3 weeks ago, and a urine pregnancy test today is negative. She and her male partner use condoms most of the time. She has mild lower abdominal tenderness, and a bimanual examination elicits mild cervical motion tenderness. The examining clinician performs a speculum examination, obtains samples for wet mount preparations and NAAT, and initiates empirical treatment with antibiotics. Which one of the following additional findings, if present, will increase the specificity of the suspected clinical diagnosis in this patient?

A. History of treatment for gonorrhea in her sexual partner.
B. History of recurrent bacterial vaginosis in the patient.
C. Cervical ectropion on speculum examination.
D. Cervical friability on speculum examination.
E. A wet mount examination that reveals clue cells.

5. A 15-year-old girl presents to the clinic with a 2-week history of lower abdominal pain and vaginal discharge. Her pain has substantially increased during the past 48 hours. Today she has vomited twice and has fever, chills, and weakness. She has had 2 male sexual partners and no female partners. At her last visit 4 months ago she was treated for symptomatic BV, and the results of NAAT were positive for chlamydia. She and her male sexual partner both received treatment with oral azithromycin 1 g in a single dose. She did not return for the follow-up visit scheduled for 3 months after treatment. Subsequent condom use has been infrequent, and she has had no new partners. On physical examination she appears uncomfortable with no respiratory distress. Her temperature is 102°F (38.9°C), heart rate is 94 beats/min, and blood pressure is 142/78 mm Hg. Abdominal examination shows bilateral lower abdominal pain with no rebound pain. On bimanual examination there is cervical motion tenderness and left adnexal pain. There is no adnexal fullness or mass. Speculum examination shows the presence of a mucopurulent discharge at the cervical os and cervical friability. Specimens are obtained for wet mount preparations and NAAT. In determining the most appropriate treatment setting for this patient, which one of the following criteria represents an indication for hospitalization?

A. Age younger than 17 years.
B. Examination findings of cervicitis.
C. History of bacterial vaginosis.
D. History of chlamydia.
E. Systemic symptoms.

INDEX OF SUSPICION

Malignant Hypertension and Osteoporotic Fractures in a 15-year-old Boy

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PRESENTATION

A 15-year-old boy with years of poor linear growth presents to the emergency department (ED) with 1 day of headache, blurry vision, and intermittent palpitations associated with elevated blood pressure (BP) (home BP using his mother's BP monitor is 181/133 mm Hg). On presentation he denies chest or abdominal pain, nausea, syncope, diplopia, dysuria, numbness, and weakness. BP at his pediatrician's office on the day before ED presentation was 190/110 mm Hg.

Several weeks earlier the patient had reestablished care with his pediatrician after a lapse of 4 years. He was seen for back pain after 2 falls from his skateboard with documented BP of 102/60 mm Hg. At that visit his weight was 98.3 lb (44.6 kg) (3.6 percentile for age), height was 57.6 in (146.3 cm) (0.1 percentile for age), and BMI was 20.8 (58th percentile for age). At age 11.5 years his weight had been 100 lb (45.4 kg) (77th percentile for age) and height had been 57 in (144.8 cm) (39th percentile for age).

On examination in the ED the patient's vital signs are notable for a pulse of 142 beats/min and BP of 193/149 mm Hg, assessed in the left upper extremity. Repeated BPs in the right upper and lower extremities are similarly elevated. The patient has flushed cheeks, bruising of the bilateral lower extremities, and Tanner II genital development. His neurologic examination findings are normal. Aside from tachycardia and hypertension, his cardiovascular examination findings are normal. His abdomen is soft, nontender, and nondistended, without palpable masses. He has truncal obesity but no abdominal striae.

Initial laboratory evaluation is significant for an elevated random serum cortisol level of 23.7 μg/dL (653 nmol/L), an elevated bicarbonate level of 31 mEq/L (31 mmol/L), a low potassium level of 2.9 mEq/L (2.9 mmol/L), and a sodium level of 145 mEq/L (145 mmol/L). Results of a complete blood cell count, renal function testing, thyroid studies, and urinalysis are normal. Electrocardiography, echocardiography, and renal ultrasonography are ordered in the ED. The patient receives intravenous hydralazine and is hospitalized in the PICU for BP management. Further diagnostic evaluation confirms the diagnosis.

AUTHOR DISCLOSURE Drs Elrokhsi, Manzo, Wheeler, Senguttuvan, and Chin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

The patient underwent extensive full-body imaging. Renal ultrasonography revealed a right adrenal mass measuring 2.8 cm but no evidence of renal artery stenosis. In the setting of hypertension and right adrenal mass, pheochromocytoma was initially the favored diagnosis for which confirmatory magnetic resonance imaging (MRI)

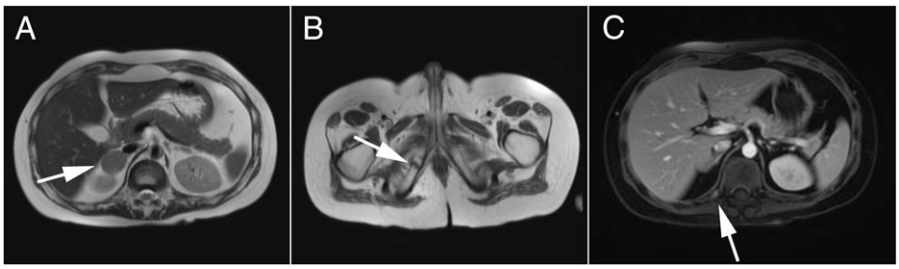


Figure 1. Presurgical abdomen and pelvis magnetic resonance images showing a right adrenal mass (A), enhancing foci in the right iliac wing (B), and the right posterior 10th rib (C).

was performed (Fig 1A). Contrast-enhancing lesions also found on MRI in the posterior fossa, left temporal lobe of the brain, ribs, pelvis, and spine were concerning for metastases. Results of an adrenal metaiodobenzylguanidine (MIBG) scan were normal.

Additional laboratory tests demonstrated an elevated 8 AM cortisol level of 23.2 μg/dL (640 nmol/L) following a 1-mg overnight dexamethasone suppression test. Free plasma metanephrine and catecholamine, urine homovanillic acid/vanillylmandelic acid, and 24-hour urine fractionated metanephrine and catecholamine levels were normal. These studies excluded pheochromocytoma. Aldosterone level of less than 3 ng/dL (<83.1 pmol/L) and plasma renin activity of less than 0.1 ng/mL per hour (<2.37 pmol/L per hour) were suppressed, which ruled out aldosterone excess.

An elevated 24-hour urinary free cortisol level of 6.02 μg/dL (166.1 nmol/L) with a urine creatinine level of 43 mg/dL (3,801.2 μmol/L) and failure to suppress cortisol levels with dexamethasone confirmed a diagnosis of Cushing syndrome (CS). He underwent total right adrenalectomy; pathology was consistent with benign adrenal cortical adenoma.

Previous imaging suggestive of metastatic disease was reviewed after the final pathology diagnosis was available. Possible bony metastases were interpreted as sclerotic healing fractures due to hypercortisolism-induced osteoporosis (Fig 1 B and C). Bone densitometry by dual-energy x-ray absorptiometry confirmed lumbar spine osteoporosis (*Z* score = –4.6). The brain lesions were believed to be posterior reversible encephalopathy syndrome (PRES) secondary to prolonged hypertension (Fig 2).

The Condition

CS is caused by prolonged exposure to excess glucocorticoids. The combination of weight gain and decreasing growth velocity in those with open epiphyses are the most frequent signs in pediatric patients with CS (1) and warrant evaluation. Classic symptoms associated with CS occur with less frequency, such as easy bruising (25% of pediatric patients with CS), facial plethora (25%), proximal myopathy (12%), and wide reddish-purple striae (61%). (1)(2) Other manifestations, such as hypertension and hypokalemic metabolic alkalosis, are less specific for CS. (3)

Among all age groups, the annual incidence of CS caused by adrenal adenoma is 0.6 per million per year. (4) The most common cause of CS is exogenous glucocorticoids. The next most common causes are corticotropin-secreting pituitary adenomas (ie, Cushing disease [CD]) in children older than 5 years and adrenocortical tumors (adenomas or carcinomas) in younger children. (2)

Diagnosis

Testing modalities for hypercortisolism include 24-hour urinary free cortisol (normal: based on assay reference range), late-night salivary cortisol (normal: ≤0.145 μg/dL [≤4 nmol/L]), or overnight or 2-day dexamethasone suppression test (normal: morning cortisol level ≤1.8 μg/dL [≤50 nmol/L]). (3) Computed tomography (CT) scans can distinguish adrenal adenomas from other adrenal tumors with greater than 90% sensitivity and specificity. (5) When lesions are characterized inadequately with CT, MRI evaluation can be considered. Nuclear medicine imaging (eg, MIBG) may be an adjunct tool. (5)

Treatment and Prognosis

Untreated CS can be fatal due to cardiovascular, thromboembolic, or hypertensive complications, or secondary to sepsis. (6) Monitoring and treatment of comorbidities is essential in CS management.

Cure by single adrenalectomy for CS caused by unilateral adrenal adenoma is nearly 100%. (7) After surgery, glucocorticoid replacement therapy must be initiated and continued until full recovery of the hypothalamic-pituitary-adrenal axis as demonstrated on a corticotropin stimulation test. Such recovery may be delayed because of secondary atrophy of the adrenal cortex in the unaffected contralateral adrenal gland.

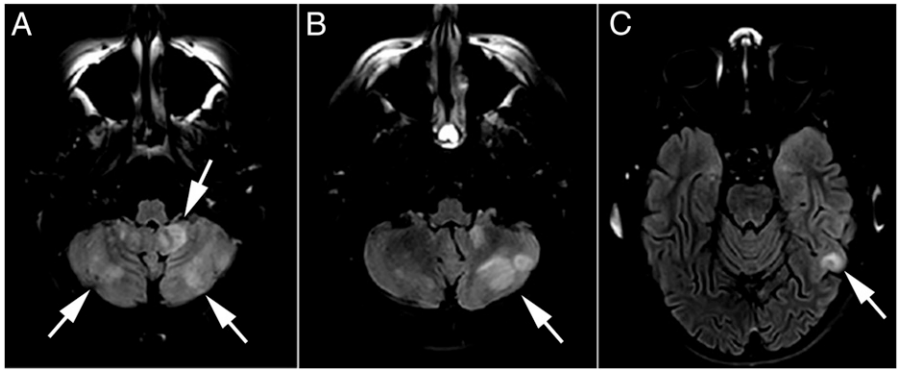


Figure 2. Presurgical brain magnetic resonance images showing vasogenic subcortical edema in the bilateral cerebellar hemispheres (A and B) and the left temporal lobe (C) consistent with posterior reversible encephalopathy syndrome.

In CS, cortisol production exceeds its inactivation, resulting in increased mineralocorticoid activity. This is manifested by hypertension and hypokalemic metabolic alkalosis. (8) Thiazides and furosemide are not recommended in the management of CS-associated hypertension because they can exacerbate hypokalemia. (8) Mineralocorticoid antagonists and ACE inhibitors are the preferred antihypertensive agents in CS. (8) Treatment of hypertension can be challenging but is imperative to minimize associated morbidity and mortality. Hypertension in most CS cases improves within 1 year after surgery. However, 21% of children with CS may have residual hypertension for more than 1 year after surgery. (9)

Case reports of PRES associated with pediatric CS have been published in the literature. (10)(11) PRES findings on neuroimaging include increased signal on T2-weighted and fluid-attenuated inversion recovery images due to white matter vasogenic edema. Posterior regions of the cerebral hemispheres are often affected, (12) and other areas of involvement include the brain stem, cerebellum, basal ganglia, and anterior hemispheres. (13) Complete resolution of neuroimaging abnormalities is seen in most patients and may occur within 1 week. (14)

Glucocorticoid excess is associated with osteoporosis, especially in trabecular bone such as the spine. (15) Bone loss is more severe in those with adrenal CS compared with those with CD. (16) However, bone mineral density improves in both adrenal and pituitary CS after hypercortisolemia treatment. (17)(18)

Before treatment, children with CS are often shorter and heavier than their peers, resulting in an overweight or obese phenotype. (1) Growth velocity improves in the year after treatment (1) and may be better in those with adrenal CS compared with patients with CD. (19) Final height attainment has been reported to be below average in those with CD despite growth hormone therapy. (20) Whether the etiology of pediatric CS has differential effects on final adult height is unknown. Long-term studies on linear growth have been primarily composed of patients with CD.

As with height, weight and BMI improve after CS treatment. (1) However, BMI and total body fat remain persistently elevated in long-term follow-up. (17) More rarely, both pituitary and adrenal CS have been associated with low BMI and disordered eating with improvement after CS treatment. (21)(22)

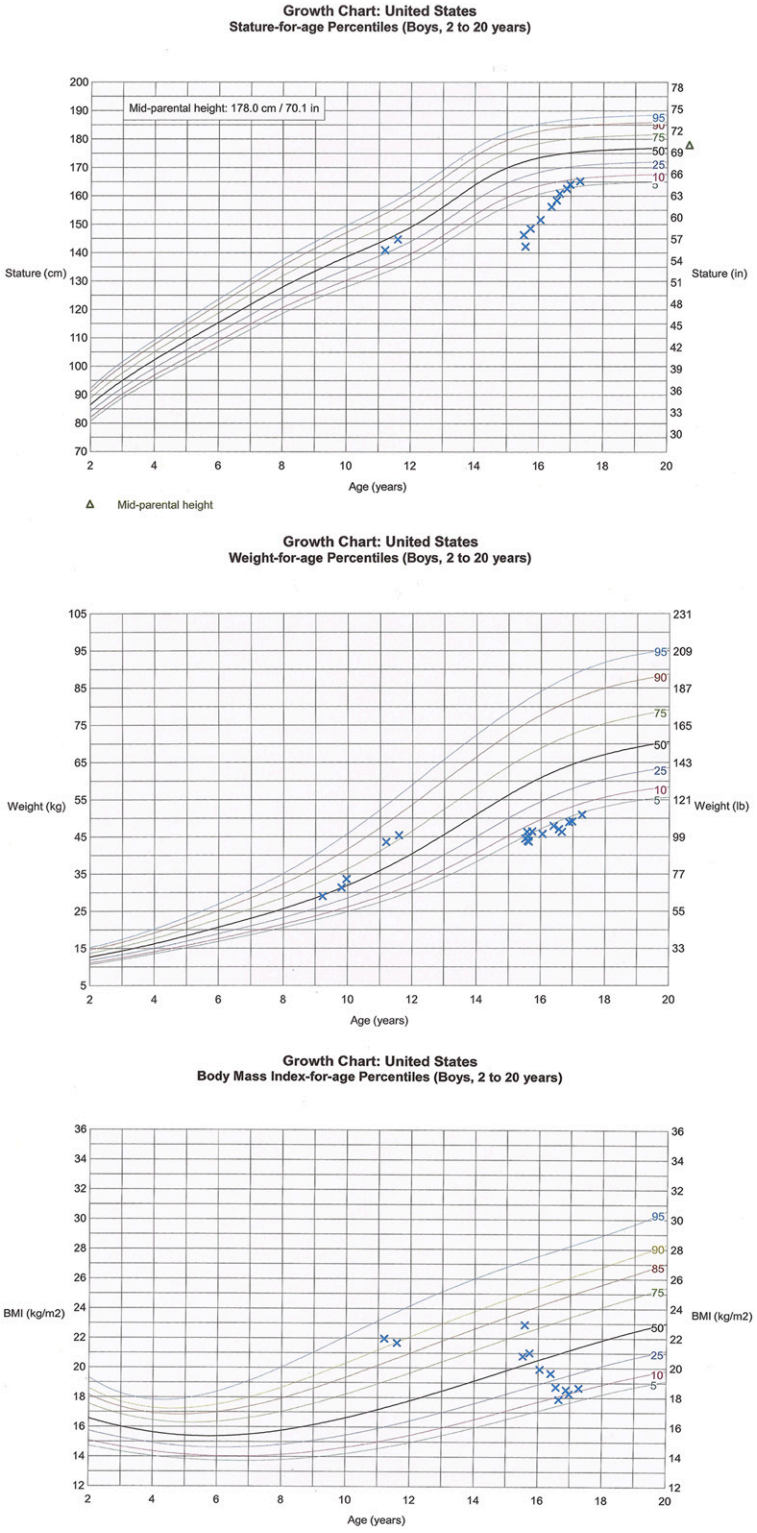
Pubertal delay has been described in pediatric CS. (1) Gonadotropin release and gonadal sex hormone secretion are inhibited by glucocorticoid excess. (23) With treatment of hypercortisolism, children with CS have normal pubertal progression. (17)

Patient Course

During hospitalization, the patient's hypertension was managed with nicardipine and nitroprusside infusions. After right adrenalectomy, the patient's hypertension quickly improved. A repeated brain MRI 3 days after surgery showed complete resolution of the enhancing brain lesions.

The patient was discharged on a hydrocortisone wean, nifedipine, a sodium-restricted diet, and supplemental calcium and vitamin D. The patient discontinued his nifedipine 2 months after discharge. Fourteen months after hospitalization, repeated dual-energy x-ray absorptiometry showed improvement in bone mineral density (lumbar spine Z score = –3.3). A corticotropin stimulation test 16 months after discharge demonstrated resolution of his secondary adrenal insufficiency. His height improved from the 0.2nd percentile for age to the 8th percentile for age over 20 months (Fig 3). His puberty has progressed normally. He was seen by a pediatric endocrinologist for 30 months after his diagnosis but was lost to further follow-up.

Figure 3. Growth curves. Growth pattern after discharge.



Lessons for the Clinician

- Regular health supervision visits with pediatricians allow recognition of early signs of serious diseases.
- Although 90% of patients with Cushing syndrome (CS) present with a history of weight gain, weight gain and obesity are not requisite features of CS; poor height growth is common.
- Cushing disease (ie, corticotropin-producing pituitary adenoma) is the most common cause of CS in older children, but adrenal causes are still possible.
- To decrease significant morbidity and mortality from CS, clinicians must keep a high level of suspicion for prompt recognition and treatment.

Note: This case is based on a poster presentation by Salaheddin Elrokhsi, MD, Mark Wheeler, MD, Rajan Senguttuvan, MD, and Cindy Chin, MD, at the Endocrine Society Meeting; Boston, MA; April 2, 2016; and on a poster presentation by Rachel Manzo, MD, Salaheddin Elrokhsi, MD, Mark Wheeler, MD, Rajan Senguttuvan, MD, and Cindy Chin, MD, at the American Academy of Pediatrics National Conference and Exhibition, Section on Pediatric Trainees Clinical Case Presentations; San Francisco, CA; October 22, 2016.

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Porencephaly and Intracranial Calcifications in a Neonate

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PRESENTATION

A baby boy with concern for ventriculomegaly on prenatal ultrasonography is born at term by urgent cesarean delivery for fetal intolerance of labor. The mother received regular prenatal care. Maternal serologic test results were normal. She denied any travel, trauma, or illness during the pregnancy. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively.

On initial examination the boy appears nondysmorphic and proportionately small, being less than the 10th percentile for weight, length, and head circumference. Neurologic examination is notable for poorly coordinated suck and nonhabituation to light and glabellar tap. The eyes are not adequately visualized secondary to periorbital edema initially; however, follow-up ophthalmologic evaluation demonstrates bilateral cataracts. The remainder of the physical examination findings are normal.

A brain magnetic resonance image is obtained to better characterize the brain abnormalities noted on ultrasonography. Large porencephalic cysts, absent corpus collosum, absent septum pellucidum, and abnormal neuronal migration are noted (Fig 1). There is well-developed cortex. Because the pattern of brain malformation is concerning for congenital infection, a head computed tomographic scan (Fig 2) is obtained to look for calcifications. The study demonstrates multiple scattered periventricular and parenchymal calcifications. Because of the intracranial calcifications (ICCs), congenital toxoplasma and cytomegalovirus (CMV) infections are specifically considered. Infant and maternal toxoplasma immunoglobulin (Ig) G and IgM are negative. Maternal CMV IgG and IgM are negative. Results of multiple urine CMV polymerase chain reaction tests for the infant are negative.

In parallel, medical genetics consultation recommends a chromosomal microarray and customized gene panel, including genes for pseudo-TORCH (toxoplasmosis, other, rubella, CMV, and herpes simplex virus) syndromes, Aicardi-Goutieres syndrome (AGS), *COL4A1*-related disorders, Smith-Lemli-Opitz syndrome, and septo-optic dysplasia.

DISCUSSION

Differential Diagnosis

The neuronal migration abnormality indicates an early brain insult, and the combination of porencephaly, well-developed cortex, and normal craniofacies suggests a late brain insult. A broad evaluation is pursued to determine a unifying

AUTHOR DISCLOSURE Dr Huang and Mr Salsbery have disclosed no financial relationships relevant to this article. Dr Steiner is an employee of PreventionGenetics, a genetic diagnostic company that performed the genetic test panel in the case described; has equity interest in and has received consulting fees from Acer Therapeutics and Censa Pharmaceuticals; has served as a consultant with compensation for Retrophin; is principal investigator of an investigator-initiated observational research study funded by Alexion via a contract with Marshfield Clinic Health System; in the past 5 years has received travel support from Pfizer and consulting fees from Raptor, Biomarin, Health Advances, Precision for Value, and Best Doctors; has served as an expert reviewer for legal cases related to malpractice claims; and has 1 patent awarded but not licensed (no revenue) and a second patent pending, both in the area of newborn screening for sterol and bile acid disorders. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

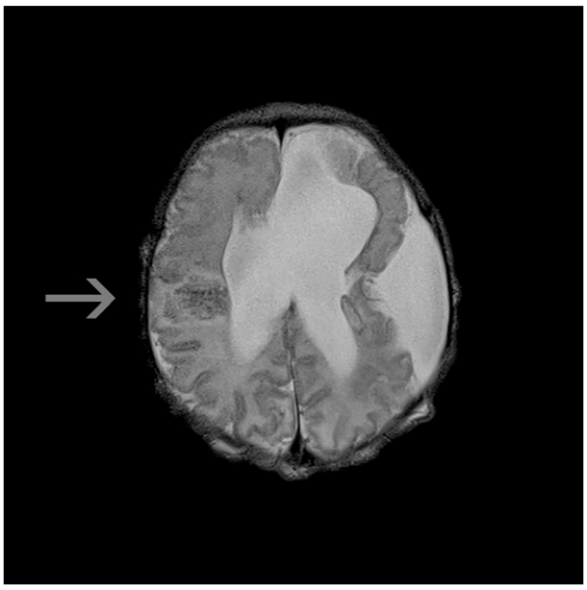

Figure 1. Axial T2-weighted magnetic resonance image of the brain demonstrating large porencephalic cysts, absent corpus collosum, absent septum pellucidum, and neuronal migration abnormality (arrow) surrounded by well-formed cortex.

diagnosis compatible with multiple insults to the brain at varying times during gestation. At the same time, the possibility of multiple etiologies is strongly considered.

Congenital infections are considered, specifically TORCH infections. The "other" category in TORCH includes syphilis, hepatitis B, varicella zoster virus, human immunodeficiency virus, parvovirus B19, enteroviruses, and lymphocytic choriomeningitis virus. (1) Clinical findings that suggest a possible congenital infection include intrauterine growth restriction, microcephaly, ICCs, rash, thrombocytopenia, hepatosplenomegaly, jaundice, and elevated transaminase levels. This boy does have intrauterine growth restriction, microcephaly, and ICCs. Imaging evidence of ICCs prompts specific consideration of toxoplasmosis and CMV. Both present with ICCs, with those associated with CMV infection classically having a periventricular distribution. However, the laboratory evaluation does not support either as the etiology.

There are, additionally, a variety of monogenic diseases that mimic congenital infections, specifically presenting with encephalomalacia and ICCs. These monogenic disorders include Pseudo-TORCH syndrome (or Baraitser-Reardon syndrome), AGS, and *COL4A1*-related disorders. Characteristic patterns of encephalomalacia and calcifications are seen in each disorder. *Pseudo-TORCH syndrome* has been used as an umbrella term to describe a phenotype of ICC, microcephaly, and the absence of infectious or metabolic etiologies. (2)(3)(4) Pathogenic variants in *OCLN* and *USP18* genes have more recently been identified as causes. (5)(6) Individuals with pathogenic variants in *OCLN* demonstrate bandlike calcifications with simplified gyration and polymicrogyria. The described phenotype for individuals with pathogenic variants in *USP18* is more variable. Individuals with AGS demonstrate early-onset encephalopathy, leukodystrophy, and ICCs. (7) These calcifications are classically of the basal ganglia but can extend into the white matter. Variants in *COL4A1* can cause a syndrome with ICCs and a wide range of small vessel brain disease, including porencephaly.

Actual Diagnosis

DNA sequencing identifies a novel, likely pathogenic, frameshift variant in *COL4A1* (c.3511_3517del, p.Pro1171Glufs*24) that causes premature protein termination. Other *COL4A1* variants causing premature protein termination have been reported to be pathogenic with similar phenotype. (8)

The Condition

The phenotypic range of *COL4A*-related disorders is wide. They are characterized by small vessel brain disease and can be associated with ocular findings and other systemic manifestations. (8) Specific ocular findings include cataracts, bilateral retinal arterial tortuosity, and Axenfeld-Rieger anomaly. Systemic manifestations include renal cysts, mitral valve prolapse, cardiac arrhythmias, Raynaud phenomenon, and muscle cramps. The small vessel brain disease can

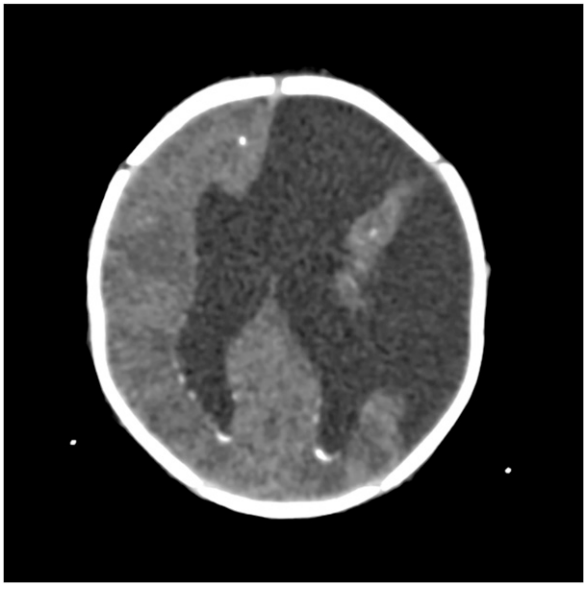

Figure 2. Axial computed tomographic scan of the head without contrast demonstrating periventricular and parenchymal calcifications.

lead to intracerebral hemorrhage and ischemic strokes at any age, even prenatally, and multiple strokes can occur over time. ICCs have been specifically described in the context of perinatal intracerebral hemorrhage and porencephaly. (9) Clinical manifestations include infantile hemiplegia, seizures, and intellectual disability.

Patient Course

As noted previously herein, this boy had bilateral cataracts. He underwent lensectomy and is currently wearing contact lenses. Echocardiography demonstrated a small midmuscular ventricular septal defect and mildly dilated chambers. Electrocardiography demonstrated prominent right ventricular forces. The dilated chambers and prominent right ventricular forces represent a high-output state likely secondary to developing anemia. The hemoglobin nadir was 7.2 g/dL (72 g/L). He did receive packed red blood cell transfusions on 2 separate occasions. The etiology of the anemia is uncertain at this time. Review of the peripheral blood smear revealed 3 to 5 schistocytes per high-powered field, which may be consistent with hemolytic anemia, as has been previously reported with *COL4A1*-related disorders. (10) Additional evaluation for occult bleeding, hemoglobinopathies, infections, red blood cell membrane, and enzyme defects was unrevealing. Abdominal ultrasonography demonstrated normal kidney morphology. On follow-up he has since developed infantile spasms, hydrocephalus requiring ventriculoperitoneal shunt placement, and failure to thrive, requiring gastrostomy tube placement. The anemia has not recurred.

Lessons for the Clinicians

- A variety of monogenic conditions may mimic congenital infections, including pseudo-TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex virus) syndromes, Aicardi-Goutieres syndrome, and *COL4A1*-related disorders.
- *COL4A1*-related disorders exhibit a wide range of phenotypes but are generally characterized by small vessel brain disease and often associated with ocular, heart, kidney, and muscle findings. The small vessel brain disease can lead to intracerebral hemorrhage and ischemic strokes at any age, even prenatally, and multiple strokes can occur over time.
- Timely clinical genetics consultation for the infant with congenital malformations may help expedite diagnosis by offering a targeted strategy for genetic testing based on the pattern of malformations.

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Altered Mental Status in a 5-year-old Girl

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PRESENTATION

A 5-year-old fully immunized girl with a history of tuberous sclerosis, localization-related epilepsy with remote resection of a seizure focus, developmental delay, oral aversion with gastrostomy tube dependence, and necrotizing pancreatitis presents with reported episodes of gait instability and altered mental status described as her head falling down, sudden diffuse loss of muscle tone, and unresponsiveness lasting 15 to 45 seconds. During the past few hours, the mother has noticed that the child appears wobbly. She had 1 episode of wobbliness with subsequent fall but denies any head injury, loss of consciousness, or tonic-clonic movements. On presentation to the emergency department she had 2 additional episodes of hypotonia and unresponsiveness to verbal stimuli lasting less than 1 minute. She had not recently missed any of her antiepileptic medications, which included levetiracetam, perampanel, vigabatrin, and taurine. In addition, her medications had not been changed in the past 6 months. Due to her oral aversion, her mother assures us that she would not have accidentally ingested any medications or other household substances.

Initial temporal temperature is 98.2°F (36.8°C), heart rate is 124 beats/min, blood pressure is 107/77 mm Hg, respiratory rate is 24 breaths/min, and oxygen saturation is 96% on room air. Physical examination reveals a wakeful crying girl fighting medical personnel and intermittently becoming hypotonic and unresponsive to verbal commands. Mucous membranes are moist, and extremities have brisk capillary refill. Respiratory effort is normal except for episodes of periodic shallow breathing. Pupils are midline and reactive but become dilated with minimal responsiveness during the episodes of hypotonia and unresponsiveness. Upper and lower extremity hypotonia is noted (with intermittent worsening during episodes), with 1+ reflexes diffusely. Cranial nerves II to XII are grossly intact. Her abdomen is soft, nondistended, and without hepatosplenomegaly, and the gastrostomy tube site does not have surrounding erythema or discharge. There are no bruises or areas of swelling.

Venous blood gas analysis revealed the following values: pH 7.33; P_{CO_2}, 57 mm Hg; base excess, 5 mmol/L; sodium, 145 mEq/L (145 mmol/L); and glucose, greater than 700 mg/dL (>38.8 mmol/L). Electrolyte testing revealed the following values: sodium, 144 mEq/L (144 mmol/L); potassium, 4.8 mEq/L (4.8 mmol/L); chloride, 104 mEq/L (104 mmol/L); anion gap, 13 mEq/L (13 mmol/L); glucose, 743 mg/dL

AUTHOR DISCLOSURE Drs Kopp, Redel, and Depinet have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

(41.2 mmol/L); and calcium, 10.5 mg/dL (2.6 mmol/L). Hematologic testing revealed the following values: white blood cell count, 14,200/μL (14.2×10^9/L) with 48% neutrophils and 44% lymphocytes; hemoglobin, 15.2 g/dL (152 g/L); and platelet count, $487\times10^3/\mu$L (487×10^9/L). Liver enzyme levels, partial thromboplastin time, prothrombin time/international normalized ratio, amylase level, and lipase level were within normal limits. Computed tomography scan without contrast of the head showed no acute hemorrhage or edema, and otherwise stable changes in a patient with tuberous sclerosis and previous surgery in the left posterior hemisphere. A blood test and urinalysis revealed the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for altered mental status is broad. The mnemonic *VITAMINS* can be helpful to remember the different causes in an acute care setting (1):

*V*ascular: stroke, inflammatory cerebritis, migraine
*I*nfection: meningitis, encephalitis, brain abscess, toxin-producing organism (eg, *Shigella*)
*T*oxins
*A*ccident/*A*buse: traumatic epidural, subdural, or diffuse axonal injury
*M*etabolic: renal, hepatic, endocrine, electrolytes, inborn error
*I*ntussusception
*N*eoplasm: tumor, hydrocephalus
*S*eizure: subclinical status epilepticus, postictal state

*V*ascular and *n*eoplastic etiologies were deemed less likely given her waxing and waning symptoms. *I*nfectious causes were unlikely without a history of fever or preceding illness. *T*oxic ingestion was unlikely because of her history of oral aversion and lack of a classic toxidrome on presentation. *M*etabolic derangements were possible given the history of necrotizing pancreatitis, but she did not have an inborn error of metabolism, any notable dietary changes, or scleral icterus to suggest a greater likelihood that this category was contributing to her symptoms. *I*ntussusception was unlikely because she had been tolerating her gastrostomy tube feeds and had no signs of abdominal pain. Therefore, the initial leading diagnoses for this particular patient were *s*eizure and traumatic head injury (*a*ccident/*a*buse) because of the sudden onset, repeated falls, and known seizure disorder.

The Diagnosis

Urinalysis showed a glucose level greater than 500 mg/dL (>27.7 mmol/L) with no ketones, and the measured serum osmolality was 365 mOsm/kg (reference range, 275–300 mOsm/kg). The profound hyperosmolar hyperglycemia without significant metabolic acidosis or ketonuria and a corrected serum sodium level of 154 mEq/L (154 mmol/L) were consistent with the diagnosis of hyperosmolar hyperglycemic state (HHS) and hypernatremic dehydration. (2) Evaluation during admission revealed lower-than-expected concentrations of endogenous insulin (1.4 μIU/mL [9.7 pmol/L]) and c-peptide (0.6 ng/mL [0.2 nmol/L]), drawn 2 minutes after a fingerstick glucose level measured 146 mg/dL (8.1 mmol/L). Her hemoglobin A1c level was 8.5%, indicating that she had chronic hyperglycemia from the insulin deficiency. Her islet cell antibody screen was negative for all 4 antibodies tested. Therefore, the diagnosis of HHS was determined to be a result of insulin deficiency secondary to necrotizing pancreatitis.

The Condition

HHS is most commonly seen in elderly patients with type 2 diabetes, but it has also been described in the pediatric population. (3) Globally, the prevalence of type 2 diabetes in children and adolescents continues to increase. (4) This may result in a relative increase in the proportion of children presenting with HHS compared with diabetic ketoacidosis (DKA). Furthermore, 2 reviews have described an increased proportion of patients with HHS having a diagnosis of type 1 diabetes. (5)(6) Therefore, it is important for pediatricians to have a high level of suspicion and accurately diagnose HHS because this can be seen in pediatric patients with either insulin resistance or insulin deficiency. The criteria for the diagnosis of HHS include the following (7): 1) serum glucose level greater than 600 mg/dL (>33.3 mmol/L), 2) serum osmolality greater than 330 mOsm/kg, and 3) absence of significant ketosis and acidosis (serum bicarbonate concentration >15 mEq/L [>15 mmol/L], urine ketone concentration less than 15 mg/dL [<1.5 mmol/L], and negative or trace ketones on urine dipstick).

Compared with DKA, there is greater circulating insulin in HHS, which minimizes ketosis but does not prevent hyperglycemia. (8) Children with both conditions will experience osmotic diuresis. However, children with DKA will develop hyperventilation, abdominal pain, and vomiting that likely prompts caregivers to seek medical evaluation sooner. Prolonged fluid losses result in children with HHS presenting with more profound dehydration and hypertonicity. (8) Children will be overall fluid depleted, but the hypertonicity from hyperglycemia in the intravascular space can mask the clinical signs of dehydration. (7) Table 1 compares the laboratory values and characteristics of patients most commonly presenting with severe DKA versus HHS. (7)(9)(10)

Table 1. Comparison of Severe Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS)

VARIABLE	SEVERE DKA	HHS
Glucose, mg/dL (mmol/L)	>250 (>13.9)	>600 (>33.3)
Arterial pH	<7.00	>7.30
Serum bicarbonate, mEq/L (mmol/L)	<10 (<10)	>15 (>15)
Anion gap, mEq/L (mmol/L)	>12 (>12)	Variable
Serum osmolality, mOsm/kg	Variable	>330
Urine ketone dipstick	Positive	Trace or negative
Average fluid deficit, % bodyweight	7–10	12–15
Type of diabetes mellitus	Type 1	Type 2
Most common age group affected	All ages	Adolescents and adults

Management

Patients should be given at least a 20-mL/kg normal saline (0.9% sodium chloride) fluid bolus over 1 hour or more quickly if needed to rapidly improve hemodynamic stability. Patients will most likely require additional boluses. After peripheral perfusion is adequately restored, patients can continue to be rehydrated with hypotonic fluids (0.45%–0.75% sodium chloride solutions) over 24 to 48 hours with a goal of decreasing the serum sodium level by 0.5 mEq/L (0.5 mmol/L) hourly. (7)

The hyperglycemia seen in HHS usually improves with fluid resuscitation alone, compared with DKA, which requires insulin. Starting patients in HHS on an insulin infusion will drive glucose and subsequently water into the intracellular space, which can precipitate intravascular collapse and cerebral edema, leading to increased mortality. The mortality rate for patients in HHS is higher than that for patients in DKA due in part to the potential for vascular collapse. Therefore, it is imperative to ensure adequate fluid resuscitation before initiating an insulin infusion, if one is warranted. It is recommended to start an insulin infusion for patients with severe acidosis, otherwise it should be postponed until glucose levels are no longer substantially declining (<50 mg/dL per hour [<2.8 mmol/L per hour]). Furthermore, the recommended insulin dose is 0.025 to 0.05 U/kg per hour, which is half of the recommended dose for DKA management (0.05–0.1 U/kg per hour). (7)

Severe electrolyte deficits are more common in HHS than in DKA. Therefore, potassium, chloride, phosphate, and magnesium levels should be obtained every 3 to 4 hours, especially if an insulin infusion is started because insulin drives potassium into cells. Additional unique recommendations include monitoring creatine kinase every 2 to 3 hours to screen for rhabdomyolysis, a rare but potentially life-threatening complication. If a patient with rhabdomyolysis develops fever, then he or she should be treated with dantrolene for presumed malignant hyperthermia-like syndrome. Central venous catheters should be avoided due to the increased risk of thromboembolism, unless required for fluid resuscitation or close monitoring. Heparin should be considered in patients with a central venous catheter, particularly if prolonged immobility (>24–48 hours) is expected. (7)

Lessons for the Clinician

- Hyperosmolar hyperglycemic state (HHS) can be seen in children with type 1 or 2 diabetes or even from other causes (eg, pancreatitis). HHS should be considered in all patients with severe hyperglycemia without a significant ketosis or acidosis.
- HHS generally requires more aggressive fluid resuscitation and electrolyte repletion compared with diabetic ketoacidosis (DKA).
- Starting an insulin infusion without adequate fluid resuscitation can lead to vascular collapse, which contributes to the higher mortality rate seen in patients with HHS compared with DKA.
- Insulin infusion initiation should be delayed until glucose levels are decreasing by less than 50 mg/dL per hour with fluid replacement alone, unless patients present with severe ketosis or acidosis, which can require earlier initiation. The dosage of insulin infusion in HHS (0.025–0.05 U/kg per hour) is half the recommended rate for DKA.

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INDEX OF SUSPICION

Strange Visual Disturbances in an 8-year old Boy

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PRESENTATION

An 8-year-old boy with no medical history presents to the urgent care clinic with complaints of strange visual disturbances over the past 2 months. The episodes are recurrent, sporadic, and transient, characterized by perceptual distortions in which objects appear faster, slower, larger, or smaller than what they should be. For example, he describes one instance when he saw abnormally large buildings and trees travel past him even though he was standing still. The episodes last 1 to 5 minutes each, and they occurred up to several times per day with increasing frequency over the last month. The visual symptoms are accompanied by loud, nondescript voices in the background. The patient is lucid and conscious during the episodes. On numerous occasions, the father witnessed his son having these events and agrees that the patient appears normal when they occur.

The patient denies any associated symptoms, including fever, headache, fatigue, aura, nausea, palpitation, or convulsion. However, he reports that he had recovered from a mild, dry cough 2 weeks before development of the visual disturbances. The cough lingered for 2 weeks before clearing on its own. Besides this, he denies any other illness, injury, or toxic ingestion. The family history is notable for schizoaffective disorder in the mother. The interview reveals a pleasant and insightful boy, who describes the events without apparent distress. The physical examination findings are otherwise normal, except for scattered crackles on lung auscultation. Based on the preceding cough and examination finding, the patient is treated with azithromycin for suspected *Mycoplasma pneumoniae* pneumonia. The visual symptoms disappear within 3 days after the antibiotics are administered.

DISCUSSION

Diagnosis

The perceptual disturbances described by the patient are consistent with Alice in Wonderland syndrome (AIWS). Similar to the illusions experienced by the title character in the fairy tale *Alice's Adventures in Wonderland*, patients with AIWS demonstrate altered perceptions of sound, space, and time, thought to be due to abnormal cerebral blood flow in the temporal and occipital lobes, where vision, texture, size, and shape, are processed. (1) The episodes are usually brief and self-limited and can occur multiple times in a day. School-age children are frequently affected, and the typical age at presentation is 8 years old. (2)(3) Although the exact cause is uncertain, infection is sometimes implicated.

AUTHOR DISCLOSURE Drs Chan and Lerner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Given the history of cough and respiratory findings on examination, the patient was diagnosed as having AIWS secondary to presumptive *M pneumoniae*. The time course of symptoms, from the cough to the visual symptoms, was consistent with the wide clinical spectrum and variable clinical course often seen with *M pneumoniae*. The prompt resolution of the visual symptoms after antibiotic drug treatment supported our suspicion. Although laboratory testing could have confirmed the presence of *M pneumoniae*, this was not pursued after discussion with the family. For this reason, we could only speculate that the AIWS was from *M pneumoniae*.

Atypical pneumonia by *M pneumoniae* is the most common form of pneumonia in school-age children. (3) It classically presents with a prodrome of fever, fatigue, and headache, followed by a protracted course of a nonproductive cough that is usually mild and self-resolving. Although primarily a respiratory illness, *M pneumoniae* infection can also cause extrapulmonary manifestations involving the skin (maculopapular and vesicular eruptions, erythema multiforme, Stevens-Johnson syndrome), blood (hemolytic anemia), heart (pericarditis, myocarditis, pericardial effusion), and brain (aseptic meningitis, encephalitis). Although central nervous system symptoms are the most common extrapulmonary complication, we are aware of only one published report documenting the association between *M pneumoniae* and AIWS. (4)

Differential Diagnosis

AIWS is a rare but impressive phenomenon. AIWS can be an atypical variant of pediatric migraine, but symptoms usually accompany headaches. Neither the patient nor his family experienced headaches. Other inciting conditions include head trauma, epilepsy, psychosis, panic disorder, drug toxicity, and infections, such as group A streptococcus and Epstein-Barr virus. (1)(2)(5) Mental illness can resemble AIWS, but the former is more frequently associated with unstable behavior, disturbed thought processes, and older age at onset. The other diagnoses were considered but ruled out based on history.

Treatment

Treatment for AIWS is tailored to the underlying cause. Unfortunately, nearly half the cases of AIWS do not have an identifiable cause. Most cases resolve within several weeks of diagnosis, although recurrence is possible. According to one report, one-third of cases may eventually develop into migraine or seizure. (2)

In this patient, azithromycin was used to treat the underlying *M pneumoniae* infection—although we wonder about the role of the macrolide's anti-inflammatory effect on AIWS. Because we did not have definitive evidence of *M pneumoniae*, we realize that our patient's symptoms could have been the first presentation of another disorder that had yet to declare itself. The patient continued to be symptom free, without any neurologic or psychiatric problems, 12 months after his initial visit.

Lessons for the Clinicians

- Alice in Wonderland syndrome (AIWS) is a rare, visual perceptual disorder that presents with a broad differential diagnosis, including migraine, epilepsy, trauma, psychosis, and infection.
- Although most cases of AIWS are benign and self-terminating, the unusual presentation can be a source of anxiety and concern for families. A vigilant history of associated symptoms, preceding illnesses, and family history are important to determine the underlying etiology and to guide management.
- Follow-up is recommended due to risks of disease recurrence and subsequent development of a neurologic disorder, such as migraine and seizure.

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IN BRIEF

Optimizing Communication with Consultants

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In medicine, as in life, clear communication is the cornerstone of successful relationships and best patient outcomes. This is particularly important among primary care providers (PCPs) and specialists when working together in consultation for the benefit of patients. Effective communication between health-care providers is necessary to provide optimal coordinated care and to prevent discontinuity and fragmented care. It is helpful to know what PCPs most want from this interaction and what information they should share with their consultants to best achieve that goal. For specialists, it is likewise important to provide information in a manner that is clear and consistent with PCPs' goals and concerns. Ideally, the consultation occurs in a timely manner and information is relayed promptly.

PCPs may want assistance with diagnosis and evaluation, or they may ask for help with the treatment/management of a patient. They may want more education for the patient or reinforcement of the information already provided. It is key for the specialist to know the reason for the consult or to be asked a specific clinical question to be able to address the issue efficiently. The PCP should succinctly summarize the question and problems specifically for the consultant. Challenges arise when a patient is sent to the specialist without the appropriate information: the specialist needs to be told what evaluation(s) and treatment(s) have been tried and any important historical background. The consultant should not have to wade through the medical record. Even with shared medical records, it may be difficult to discern the reason for the consult and impossible to know whether the PCP prefers that the specialist take over this aspect of care, provide mutual ongoing collaboration and management, or respond with a 1-time assessment and suggestions for next steps. The specialist should also solicit further information from the patient and avoid "cutting and pasting" information from the electronic health record (EHR). When sending a postconsultation letter to the PCP, the specialist should focus on the most relevant information.

The common goal, best patient care and outcome, should be collaborative and patient-centered. Depending on the issue, patients/families may feel comfortable only with a plan that has been discussed with the PCP; others may trust and expect recommendations directly from the consultant. How do we achieve this collaborative patient-centered model, where physicians often do not have the opportunity for face-to-face communication? Structured communication and a standardized approach that is evaluated for efficacy over time is likely best. Formal training of medical students and residents on how to obtain consults, and the most useful elements to share in verbal or written communication, has been assessed and found to be helpful. One study that evaluated an online training session and then a simulated assessment revealed satisfaction among the interns trained and

AUTHOR DISCLOSURE Drs Bingemann and Garfunkel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of unapproved/investigational use of a commercial product/device.

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evaluated. Faculty felt that trained interns were more prepared than interns that were not trained. Research is ongoing, on both the interpersonal and systemic levels, to assess what are the best practice elements to be communicated when requesting a consult and which elements promote efficient, safe, and effective continuity of care. These elements will vary by specialty and by PCP knowledge and skills. They will also vary over time and with the experience of both providers. As with any improvement process, developed communication structures should be evaluated and reevaluated locally and modified to provide best care.

The most common form of PCP-specialist communication is written, in a letter, in an e-mail, or directly in the EHR. Formatting should aim for the most effective communication to meet the needs of the recipient. Unfortunately, letters are often written from the perspective of the sender and may miss details important to the receiver. Letters may include abbreviations with which the recipient is unfamiliar, leading to confusion. Multiple studies have found that the information desired by the PCP and specialist differ and suggest that a specific structure and content be developed in collaboration between PCPs and specialists as a standard or template, which may vary by specialty. Structured rather than unstructured referral requests are likely more useful to specialists and can help in the assessment of the urgency of the consultation. Conversely, less structured documents may allow the PCP to ask several questions, include psychological history, and provide what the PCP considers valuable information that the patient may not share with the specialist.

Even with the availability of a referral form or letter, it remains common for specialists to have patients appear without having first received a written communication. Moreover, even with a shared EHR it is often difficult for the specialist to ascertain the reason for a consultation. In addition, referrals may well come from providers outside the system that shares an EHR. The impact of not receiving information is less when the concern is straightforward and when the patient or family can effectively relay the reason for the visit. When the problem is more complicated or the family and patient have poor health literacy and understanding, it can be difficult for the consultant to understand the reason for the visit. Physicians themselves have strongly associated their ability to provide optimal care with effective interphysician communication. The potential barriers to communication (written and verbal) are many: the time necessary to write a referral letter or complete a standardized referral form, dictation and mail delays, letters not reaching the correct consultant in a group practice, incorrect uploading of the letter into the recipient's system, other human errors and delays (at both sites), and phone access and triage system difficulties.

In a study of communication breakdown in the outpatient referral process at one academic center, lack of timeliness in communication and inadequate information in referral letters were identified as problems. Generalists and specialists agreed that the reason for referral, identification of the problem, and current medications should be included in the referral. The information identified that the specialists wanted from the PCPs included the problem or question to address, details that the patient was not likely to provide, other medical problems, and medications. Having the essential information available when the consultation is requested can better enable the specialist to schedule the patient in an appropriate time frame. This may increase visit efficiency by allowing the consultant to provide a more complete plan at the time of the visit and to spend time counseling. In turn, this may increase the quality of the visit, aid in disease management, and increase patient satisfaction. The most important information that PCPs wanted from specialists was results of pertinent tests and procedures, therapy proposed or initiated, answers to their specific questions, and the assessment of the patient. It is important that specialists communicate with PCPs in a timely manner, addressing the specific questions asked and suggesting ongoing evaluation or management as the PCP desires. The specialist may need to contact the PCP urgently to address issues that the specialist feels need to be addressed promptly or to clarify the reason for the consultation if it is not clear.

Clear communication and respectful relationships are necessary to provide the best care. Clear communication includes the reason for the consult, its urgency, how the PCP (or inpatient generalist/hospitalist) would like information shared, and whether the referring physician would just like the answer to a specific question or would like the consultant to co-manage or to take charge of the care for the referral issue. Outpatient consultations may have a different acuity from inpatient consultations and pose different challenges. In the outpatient setting, providers are often in separate locations that limit face-to-face interactions, and relevant patient information, the reason for the consult, and a way to reach the PCP with questions are not always readily available. Whether outpatient or inpatient, when the reason for the consultation is emergent the referring physician should reach out directly to the consultant either in person or by telephone, and the specialist should make every effort to respond immediately.

We need to speak the same language as our collaborating caregivers as well as the families we serve. Using a cooperatively designed template, agreed on by referrer and

consultant, with elements that are of greatest value to both, can minimize work and add value. The template's exact elements will vary by specialty; however, the reason for the consult, an account of the evaluation and treatment before referral, and a list of medications and other medical problems will be relevant for all. Despite recent technological advances, sometimes the best approach is to pick up the telephone to discuss the patient directly with other members of the care team.

COMMENT: Personal communication really is essential to an effective referral process, and sometimes that communication should begin even before the formal referral is made. Speaking (whether by voice or electronically) with an orthopedist before sending on a patient may expedite the intended visit by having the patient undergo any needed imaging before first being seen. Likewise, learning beforehand what specific laboratory tests a rheumatologist may want based on a patient's presentation will make the referral visit more efficient.

More delicate when considering a consultation is communicating with the family what the cost to them may be. By the latest available data, in 2018, 27.5 million Americans had no health insurance, and many more were underinsured, with medical debt totaling more than $80 billion. Even with the Children's Health Insurance Program, more than 4 million children were uninsured. Referrals can bring with them significant expenses, and families need to know.

–Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR OCTOBER 2020 PEDIATRICS IN REVIEW

Infections after Natural Disasters: 1. E; 2. A; 3. E; 4. D; 5. E.
Pancreatitis: 1. D; 2. C; 3. E; 4. D; 5. D.
Sexually Transmitted Infections Part 2: Discharge Syndromes and Pelvic Inflammatory Disease: 1. E; 2. A; 3. D; 4. D; 5. E.

IN BRIEF

#TechAddicted: Understanding Problematic Internet Use in Adolescents

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With the increasing availability and use of digital and electronic media, researchers have increasingly focused on quantifying its healthy and unhealthy uses. From this effort have emerged tools to define and detect problematic use of media and technology. The vast majority of this research and related tools pertain specifically to media that are connected to the Internet, such as online gambling, Internet gaming, and social media. Problematic Internet use (PIU) has become an important public health issue among adolescents, and thus it is relevant to pediatricians.

Early work and definitions of electronic addiction focused on the concept of Internet addiction. Definitions of Internet addiction were directly translated from the diagnostic criteria associated with other types of addiction, such as alcohol use disorder. Most models of Internet addiction include symptoms associated with substance misuse, such as using the Internet to regulate one's mood or loss of control while using the Internet. Somewhat lacking from this framework, however, has been an acknowledgment that use of the Internet can be problematic and clinically significant in the absence of outcomes or features traditionally associated with addiction to chemical substances.

In the past decade, PIU has emerged as the preferred construct in the literature and in clinical settings. In contrast to the narrow focus of Internet addiction, PIU has been defined as "internet use that is risky, excessive or impulsive in nature, leading to adverse life consequences, specifically physical, emotional, social, or functional impairment." (Moreno et al., 2013) In a clinical setting, use of the construct PIU has at least two major benefits. First, it acknowledges that impairment or negative life consequences may result from the problematic use of media without otherwise resembling addiction as it is traditionally conceptualized. And second, the measurement tool associated with PIU, the Problematic and Risky Internet Use Screening Scale (PRIUSS), is not specific to one electronic medium, giving it broader clinical utility and relevance over time. The PRIUSS can detect PIU overall and can also detect problematic use of subtypes of electronic media, such as video games, social media, gambling, and the use of smartphones. Furthermore, the PRIUSS remains the only validated English language screening tool with a robust evidence base in the scientific literature.

Prevalence estimates for PIU vary by population. With the PRIUSS as a measurement tool, prevalence has ranged from 9% to 11% in college samples in the United States. Subsets of PIU have shown somewhat different prevalence rates. For example, Internet gaming disorder has shown rates of 1.16% in German adolescents and 10.8% in Korean adolescents. Social media addiction (as measured by the Bergen Social Media Addiction Scale) showed a prevalence of 4.5% among Hungarian

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adolescents. Measurement of PIU is complicated by research showing that people may not accurately report their own Internet use.

Despite the challenges in reporting, assessing, and understanding PIU, efforts have been made to articulate (and, ultimately, prevent) its development in the individual. Why is it that in today's digitally immersed society, some people develop PIU and others do not? As with other mental health disorders, the answer must account for dispositional and environmental factors. At least two primary environmental mechanisms have been posited. One suggests that Internet use that is in its nature excessive leads to the development of PIU, regardless of the specific activities performed online. Another suggests that particular types of Internet use (eg, viewing pornography or engaging with social media) promote addiction, because these activities may trigger the release of dopamine or are otherwise particularly rewarding. Similar to the development of other behavioral addictions, much work remains to be done before the genesis or mechanisms of PIU are understood.

Just as the process of development is an outstanding question, so is the question of who is most at risk. Studies are conflicting in this area. Some suggest that females are more at risk for PIU, and others suggest that the same is true for men and older teens. PIU is more common in people with other comorbid mental and physical health conditions, including attention-deficit/hyperactivity disorder, depression, and social anxiety, as well as sleep difficulties, reduced physical activity, and less healthy eating. Research suggests that socioeconomic status is also associated with PIU; it may be that for adolescents in less privileged homes, parents are not available to actively monitor the media use of their children.

Treatment for electronic addiction resembles treatment for other behavioral addictions and may include extended periods of time without the medium and development of new, healthier replacement behaviors. Unfortunately, no evidence-based treatment approaches for PIU are currently available in the United States. Given the difficulty and cost associated with treating any behavioral addiction, prevention is paramount and starts at home. Parents should be encouraged to model the appropriate use of media for their children as well as to set explicit boundaries around media engagement. The American Academy of Pediatrics (AAP) has put forth guidelines on media use, which include limiting both the amount of screen media use and the types of media used, as well as encouraging families to identify media-free times and locations in the home:

1. For children younger than 18 months, avoid screen media (other than video-chatting).
2. Limit screen use to 1 hour per day of high-quality viewing for children 2 to 5 years old.
3. For older children and adolescents, put consistent limits on the time and types of media use, making sure it does not interfere with adequate sleep, physical activity, and other age-appropriate healthy behaviors. Designate media-free times (dinner and driving) and media-free areas (bedrooms). Have ongoing conversations about online safety and treating everyone with respect.

The past decade has seen enormous strides in defining and understanding PIU, particularly in conceptualizing PIU as a broader, more clinically relevant concept compared with Internet addiction. Significant areas of need for future research include appropriate prevention and intervention strategies. Two key tools available for clinicians include 1) the PRIUSS for use in primary care settings and 2) the Family Media Use Plan, a tool derived from the AAP's 2016 media use guidelines. This tool can empower families to define and develop personalized strategies for healthy media use at home.

COMMENT: Prevention is, of course, far preferable to treatment. The AAP 2016 Guidelines on Media Use emphasize the role parents must play in supervising their children's engagement with electronic media, both in setting limits and in actively encouraging conversations that can lead to mutual understanding. But experience should warn us that powerful forces beyond the family's reach are involved. The tech companies behind social media, Internet gaming, online gambling, and the such have a vested interest in promoting the use of their products, as did tobacco companies and, more recently, the vaping industry. Profits are the bottom line. Product design as well as advertising are designed to attract customers, and children and adolescents are an attractive and lucrative target. Once again, we need active advocacy by the pediatric community, individually as well as through the AAP, in pushing for regulation of the ever-expanding tech world now seemingly omnipresent, but hopefully not yet omnipotent.

–Henry M. Adam, MD
Associate Editor, *In Brief*

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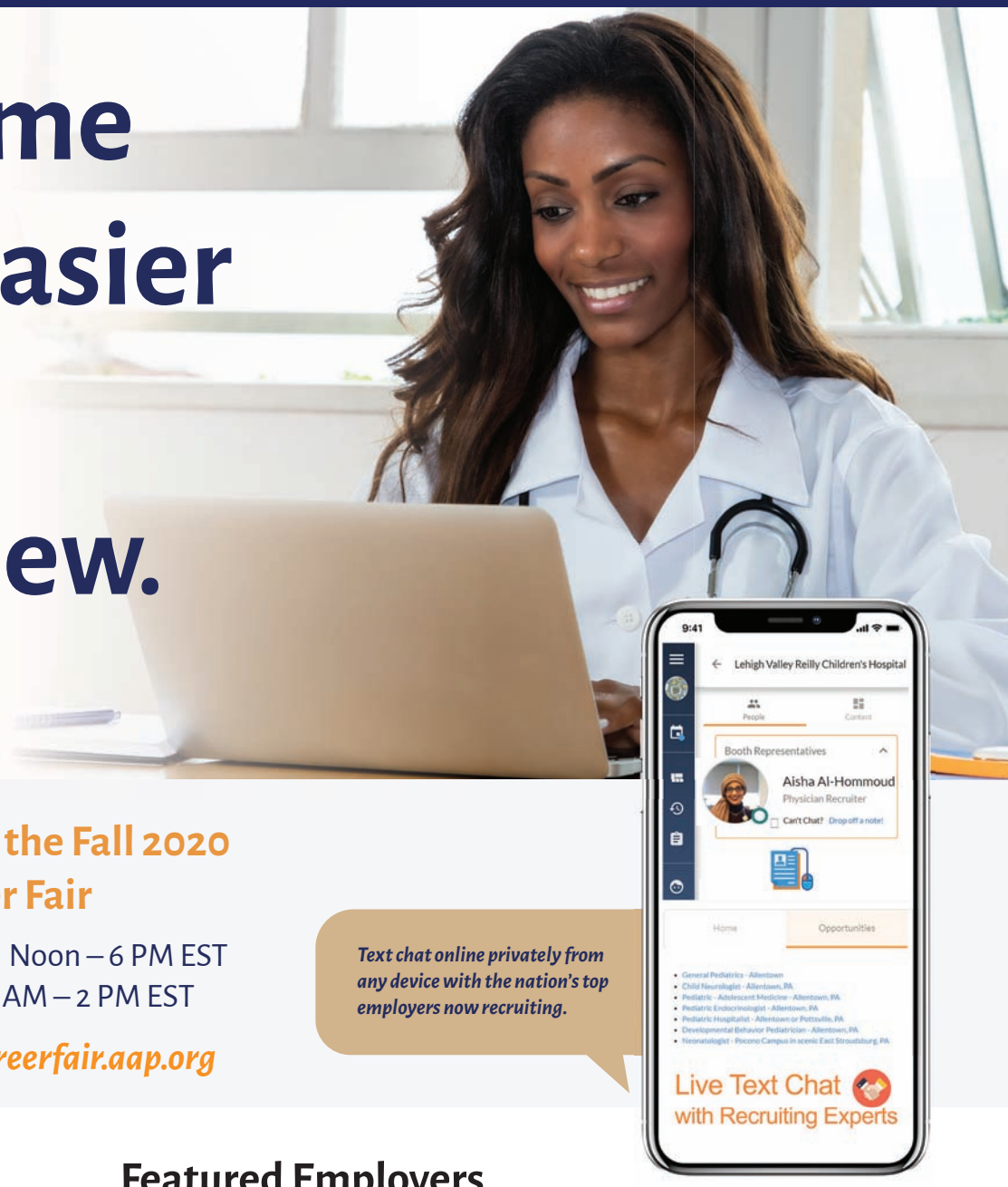

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VISUAL DIAGNOSIS

Rapid Deterioration of Respiratory Status and Lower Limb Hypotonia in a 6-month-old Infant

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PRESENTATION

A 6-month-old previously healthy boy presents to the local emergency department with a 1-week history of progressive lethargy, irritability, and anorexia. Two days before presentation he developed an unusual breathing pattern and worsening respiratory distress, and he had a fever of 101.3°F (38.5°C). There was no rhinorrhea, coryza, cough, vomiting, or diarrhea.

He appears unwell, with respiratory distress, tachypnea, and grunting. His blood pressure is 80/45 mm Hg, heart rate is 200 beats/min, respiratory rate is 60 breaths/min, and oxygen saturation is 77% in room air. He is afebrile. There is significantly decreased air entry bilaterally, most impressively over the right lung field. His neurologic examination reveals a mild right-sided ptosis. Although he moves both arms normally, there is a noticeable paucity of movements in his lower limbs, with decreased tone in both legs. The remainder of his examination findings are normal.

On further questioning the parents clarify that for the past 2 months there has been a relative decrease in leg movements, and he had stopped attempting to bear weight when made to stand with support.

His respiratory status does not improve, and he requires supplemental oxygen to maintain appropriate oxygen saturation. Clinical laboratory tests reveal a white blood cell count of 18,800/μL (18.8×10^9/L) (neutrophil count, 6,200/μL [6.2×10^9/L]; lymphocyte count, 11,100/μL [11.1×10^9/L]; and monocyte count, 1,100/μL [1.1×10^9/L]) and normal electrolyte levels. A chest radiograph reveals a large right paravertebral mass with significant left mediastinal shift associated with rib and vertebral destruction and moderate right-sided pleural effusion (Fig 1). Given these findings and worsening respiratory distress, the patient is urgently transferred to a pediatric tertiary care center.

He is admitted to the PICU and a chest tube is inserted, draining serosanguinous fluid. Computed tomography scans (Fig 2) show an extensive mass extending from the carina down to the diaphragmatic crus bilaterally, with mass effect on multiple vascular structures and multifocal rib involvement. Magnetic resonance imaging (Fig 3) shows the lesion in the posterior mediastinum extending from T12 to L1 and infiltrating the spinal canal at multiple levels through the right-sided neural foramina between T5 and T10 causing severe compression and displacement of the spinal cord.

DIAGNOSIS

The differential diagnosis of posterior mediastinal mass is broad and includes neuroblastoma, rhabdomyosarcoma, lymphoma, and members of the Ewing sarcoma

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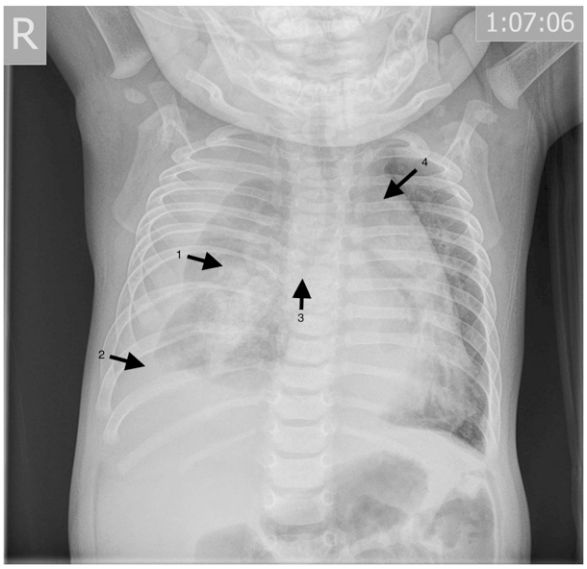

Figure 1. Initial anteroposterior chest radiograph shows a right paravertebral mass (arrow 1) associated with moderate right-sided pleural effusion (arrow 2), rib and vertebral destruction (arrow 3), and left mediastinal shift (arrow 4).

family of tumors, including Ewing sarcoma, extraosseus Ewing tumor, and neuroepithelioma, also called primitive neuroectodermal tumor. Clinical features and a variety of light microscopic, electronic microscopic, and immunochemical characteristics are useful in differentiating these. The age of our patient makes the Ewing sarcoma family of tumors unlikely as they very rarely occur at younger than 4 years and are more frequently found in adolescents. (1)

Urine catecholamine metabolite levels reveal elevated vanillylmandelic acid and homovanillic acid. A biopsy of the paravertebral mass demonstrates characteristic small round blue cells, which, along with elevated urine catecholamine metabolites, confirms the diagnosis of neuroblastoma.

DISCUSSION

Neuroblastoma is a neuroendocrine tumor arising from primitive sympathetic ganglion cells. It is the most common extracranial solid tumor diagnosed in infants younger than 12 months, and the third most common childhood cancer, after leukemia and brain tumors. (2) The median age at diagnosis is 17 months. (3)

Neuroblastoma is notoriously heterogeneous in its clinical behavior. The initial presentation and course vary greatly according to the site of the primary lesion. Because it originates from ganglion cells, these tumors may arise at any location throughout the sympathetic nervous system. The most common primary site is the adrenal glands, accounting for 40% of all cases. (4) They may also arise from the ganglia along the paraspinal sympathetic chain: at the abdominal (25%), thoracic (15%), cervical (5%), and pelvic (5%) ganglia. (4)

When these tumors arise from thoracic sympathetic ganglia, the initial presentation may be respiratory distress, as was the case with our patient. Large thoracic tumors can cause mediastinal shift, superior vena cava syndrome, (5) and Horner syndrome, (6) which may explain the noted right-sided ptosis in our patient's initial presentation. Because these masses are paravertebral, they may invade the spinal canal through the neural foramina and cause spinal cord compression, presenting as motor or sensory deficits, pain, and loss of bowel or bladder control. (7) In young infants such as our patient, a detailed neurologic examination is often challenging, but evidence of deficits may be ascertained through careful observation and a thorough history of their behavior from the parents. For confirmatory assessment of spinal cord compression, MRI remains the modality of choice, with sensitivity of 93%, specificity of 97%, and overall diagnostic accuracy of 95%. (8)

Neuroblastoma is associated with elevated catecholamine levels, but, in contrast with pheochromocytoma, hypertension is uncommon. Severe hypertension has been reported in patients who have neuroblastoma tumors impinging on the renal vasculature, but this remains rare. (9)

Measurement of urine catecholamine metabolites is an important component of both the diagnostic evaluation of neuroblastoma and the monitoring of disease response to treatment. Due to the origin of neuroblastoma and related neuroendocrine tumors of neural crest cells, most of these tumors express the enzymes present in the metabolic pathway of norepinephrine and dopamine and can, therefore, uptake and break down catecholamines. 3-Methoxy-4-hydroxymandelic acid (vanillylmandelic acid) and 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid) are major end products of norepinephrine and dopamine metabolism, respectively, and elevations can be detected in both urine and serum. Urinary excretion of these metabolites has been found to be elevated in at least 75% of patients with neuroblastoma and related tumors of neuroendocrine origin. (10) The definitive diagnosis of neuroblastoma is established by either unequivocal pathologic diagnosis from tumor tissue with or without increased urine catecholamine metabolites or unequivocal tumor cells in bone marrow and increased urine catecholamine metabolites, defined as at least 2 metabolites measured at more than 3 SD above the mean per-milligram creatinine level for age. (11)

As part of this metabolic activity, neuroblastoma tumors also express the norepinephrine transporter gene *(NET)* for extracellular reuptake of norepinephrine and dopamine.

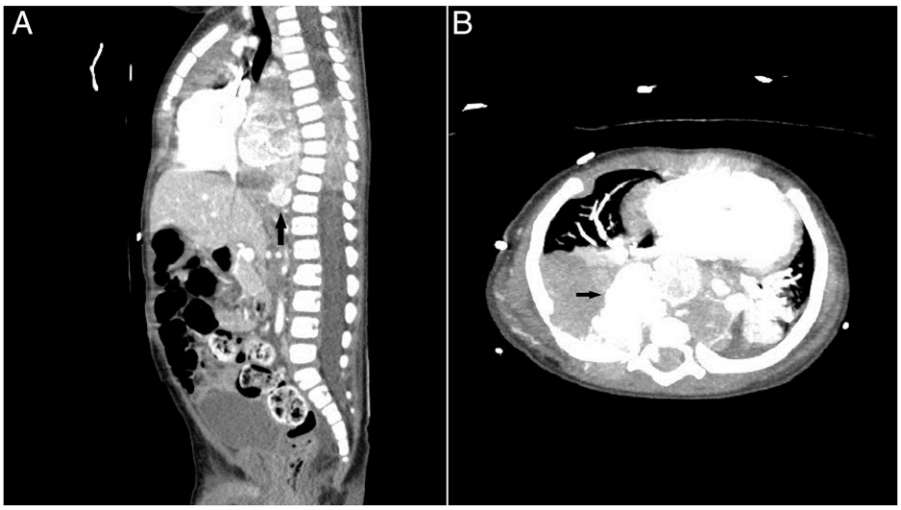

Figure 2. Computed tomography scans. A. Sagittal view shows an extensive polylobulated, prevertebral soft tissue mass (broad arrow) extending from the carina down to the level of the diaphragmatic crus. The soft tissue mass shows components of calcification with clusters of nodular calcification and peripheral linear calcifications. B. On transverse view, the round soft tissue mass (small arrow) is noted at the right anterior mediastinal outline. Hyperintensity in the spinal cord represents extension of mass, which is best described in magnetic resonance imaging (Fig 3).

NET expression also allows for active cellular uptake of metaiodobenzylguanidine (MIBG), an analog of epinephrine, which can be radiolabeled and specifically taken up by tissues of the sympathetic nervous system. (12) I^{123}-MIBG scans are sensitive and specific for neuroblastoma and are recommended for diagnostic evaluation and follow-up. This modality is particularly useful for evaluation of bone metastases and is preferred over technetium scan due to greater sensitivity and specificity. (13) Assessment for distant metastases is required with any new diagnosis of neuroblastoma; in our patient's case, the MIBG scan showed no evidence of metastatic spread, although, as expected, the primary tumor demonstrated uptake of MIBG.

Presence of bone marrow involvement must also be evaluated through aspiration and biopsy at the posterior iliac crests. Positive tumor or bone marrow tissue then require further evaluation for status of the *MYCN* gene. Amplification of the *MYCN* gene, a proto-oncogene of the MYC family of transcription factors, is an independent prognostic factor for rapid tumor progression and poor prognosis in patients with neuroblastoma. (14) *MYCN* amplification is defined as the presence of greater than 10 copies of the *MYCN* gene. Our patient's bone marrow biopsies and aspirates were negative for malignancy, and there was no evidence of *MYCN* amplification on biopsy of the primary lesion. Along with a favorable histology report, this placed our patient in an intermediate-risk category according to the International Neuroblastoma Risk Group Staging System. (15) This consensus classification schema uses the age of the patient, staging, histologic category, grade of tumor differentiation, *MYCN* status, chromosome 11q status, and tumor cell ploidy to stratify risk according to event-free survival. Ploidy refers to alterations in the total DNA content of tumor tissue as approximated by measurement of the DNA index by flow cytometry. Neuroblastomas with a DNA index greater than 1, also called hyperdiploid, have been associated with an improved prognosis over diploid tumors with a DNA index of 1. (16) This association seems to be age dependent because it has been observed only in children younger than 2 years. (17) The intermediate-risk category, in which our patient falls, is associated with a 5-year estimated event-free survival rate between 50% and 75%. (15)

Locally invasive tumors are unresectable at diagnosis, and management under the intermediate-risk stratification involves chemotherapy followed by surgical resection if consequently resectable. Patients with intermediate-risk neuroblastoma typically are younger than 18 months with locally invasive tumors and favorable biology (*MYCN* not amplified and DNA index >1), such as our patient. These patients have excellent overall survival (>90%) with 4 to 8 cycles of carboplatin, etoposide, doxorubicin, and cyclophosphamide and resection of the primary tumor. (18) In contrast, low-risk category neuroblastomas are treated through resection alone, and high-risk tumors receive an aggressive multimodality approach with high-dose chemotherapy, surgical resection, and radiotherapy. Childhood neuroblastoma survivors generally continue to be followed by a pediatric oncologist for disease recurrence and persistent toxicity, with the frequency of visits decreasing over time.

Spinal cord compression in neuroblastoma can cause long-term neurologic sequalae. Emergent treatment is, therefore, required because early decompression may prevent irreversible neurologic deficit. Optimal treatment is debatable, with options including surgical decompression, radiotherapy, and chemotherapy. Laminectomy has particularly been associated with spinal instability, and it has been demonstrated that there are equivalent neurologic outcomes for patients treated with chemotherapy or laminectomy. Chemotherapy is favored

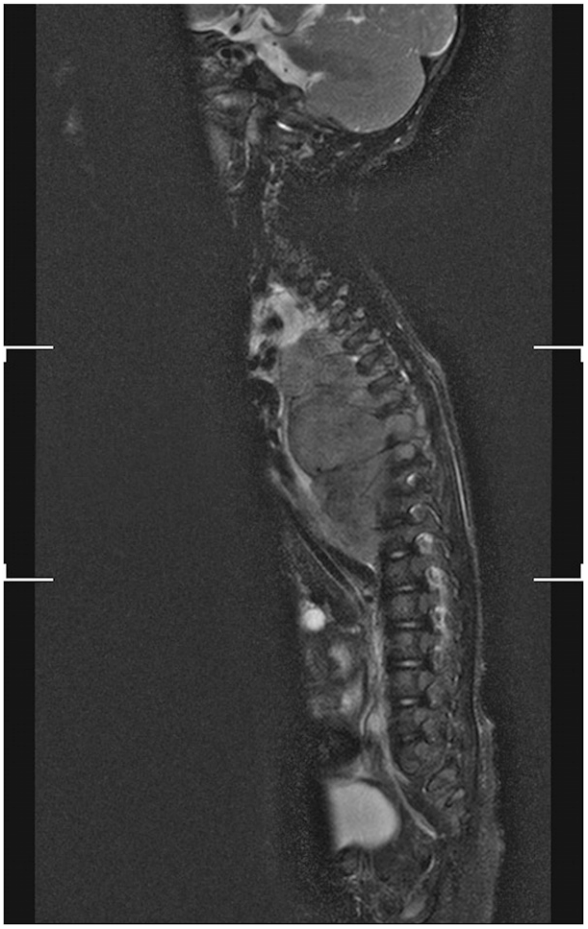

Figure 3. T2-weighted magnetic resonance image in the sagittal view shows a large lobulated mass in the posterior mediastinum extending from approximately T12 to L1. The mass extends into the spinal canal at multiple levels through multiple right-sided neural foramina at T5 to T10 with a large intraspinal component causing severe compression and displacement of the spinal cord. There is abnormal T2 signal hyperintensity in the cord immediately above and below the level of the tumor.

because it avoids the possible long-term sequelae of laminectomy or spinal irradiation, with similar or improved recovery of neurologic functions. Dexamethasone has also been shown to be of benefit in reducing edema and inflammation. (19)

PATIENT COURSE

The patient is started on intravenous dexamethasone and emergent chemotherapy with carboplatin and etoposide. Pathologic analysis confirms neuroblastoma with no evidence of *MYCN* oncogene amplification and favorable histologic findings. A staging I^{123}-MIBG scan shows no evidence of metastatic spread, although the primary tumor itself is MIBG avid. Bilateral bone marrow biopsies and aspirates are negative for malignancy.

His respiratory status improves during admission. He is weaned off oxygen, and his chest tube is eventually removed. He is discharged in stable condition with routine follow-up for chemotherapy as an outpatient. He is treated as having an intermediate-risk neuroblastoma and responds well to a single course of chemotherapy, receiving 4 cycles of carboplatin, doxyrubicin, and etoposide in addition to the emergent treatment. Excisional surgery via thoracotomy is successfully performed 3 months after the initial presentation. He remains off chemotherapy after his surgery.

Our patient continues to receive long-term follow-up and has remained disease free since his surgery. Fortunately, he has made a full neurologic recovery.

Summary

- Neuroblastoma is the third most common childhood cancer. The presentation and course vary greatly based on the site of the primary lesion. It may arise at any location throughout the sympathetic nervous system, including the adrenal glands and ganglia along the paraspinal sympathetic chain.
- Neuroblastoma can present with rapid deterioration of respiratory status and neurologic defects due to spinal cord compression.
- The diagnosis of neuroblastoma is established by either pathologic evaluation of tissue with or without increased urine catecholamine metabolites or identification of tumor cells in bone marrow with increased urine catecholamine metabolites. An I^{123}-metaiodobenzylguanidine scan establishes the presence or absence of distant metastases.
- Neuroblastoma is classified as low, intermediate, or high risk based on age, stage, histopathologic findings, *MYCN* amplification, and DNA index (ploidy).

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