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Some definitions to start. Fever VS Hyperthermia

- Fever (usually >38°C) is an elevation in core body temperature seen in infections, autoimmune, autoinflammatory diseases
- Hyperpyrexia (>41.5° C) is seen in severe infection or CNS hemorrhage
- Hyperthermia (can be **fatal**): Thermoregulatory center unchanged despite increasing temperature

On history, definitely ask about: exposure (sick contacts), recent travel, B symptoms, recent changes to medications, surgical history (especially surgeries in the past 2 weeks), prosthetic joints/valves/grafts they may have, IVDU and STI exposure. Don't overlook dental infections.

On physical exam, keep an eye out for rash, conjunctivitis, uveitis (autoimmune), hepato-splenomegaly, any joint swelling and lymphadenopathy

Red flags for fever that should make you concerned include:

1. Change in HR and BP, we're talking SIRS Criteria here. SIRS Criteria need at least 2 of 4 of: body temperature >38 or <36, HR>90, RR>20 or PaCO2 <32 mmHg, and WBC >12 or <4
2. Newborn 0-3 months old
3. Tachypnea
4. Mental status change, headache and nuchal rigidity
5. Fever > 3 days

Objective 1

In febrile infants 0-3 months old:

- **Recognize the risk of occult bacteremia.**
- **Investigate thoroughly (e.g., blood cultures, urine, lumbar puncture +/- chest X-ray).**

In this population, rectal temperature is the only form of reliable measurement of measuring temperature. Axillary, tympanic, and temporal artery measurements have been shown to be unreliable.

Signs of serious infection include: lethargy, cyanosis, poor peripheral circulation, petechial rash (indicative of Neisseria meningitidis), and inconsolability

Risk Factors for sepsis include prolonged rupture of membranes (>16 hours), maternal intrapartum fever, Group B Strep without prophylactic antibiotics (previous pregnancy, positive GBC swab, GBS bacteriuria), and born <37 weeks. Of note, prophylactic antibiotics only decrease the risk of early GBS sepsis. The risk of late GBS sepsis remains the same.

The investigations you want to do are: CBCd, blood cultures, lumbar puncture, UA/UC and CXR.

If patient is hemodynamically unstable, defer LP. Don't delay antibiotics to try to get LP. Beyond 1 month consider NPA for respiratory viruses, joint fluid and stool cultures based on the symptoms of the patient

Empiric antibiotics at meningitis dosing will be differ based on age:

- For < 7 days -> Usual pathogens are: GBS, E coli, MSSA/MRSA, CONS. Less common are Listeria spp, H flu, Enterococcus spp, HSV
- Ampicillin (cover GBS and Listeria) and gentamicin (for gram negatives), Add acyclovir if HSV is on your differential and vancomycin if MRSA/enterococcus are suspected. Can see neonatal HSV up to 6 weeks of age.
- For fever 1 – 3 months, Cefotaxime +/- vancomycin, add vanco if suspicious for meningitis
- For >3 months, Ceftriaxone and +/- vancomycin, add vanco if suspicious for MRSA or enterococcus meningitis
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OR

Use the pediatric assessment triangle (PAT) to quickly assess patients who need immediate supportive care.
The PAT relies on 3 observations: appearance, breathing and circulatory status. An ill patient is defined by abnormalities in one or more of these 3 areas. The golden ABCs

- For appearance we're assessing tone, interactiveness, consolability, look/gaze and speech or crying (is it loud and strong, or weak and muffled)
- For breathing we're listening to the airway looking for stridor, snoring, grunting, and wheezing (things that indicate respiratory distress), positioning (Tripoding or "sniffing position" (which is neck flexed, head mildly extended to align the airway axes and improve airflow) and accessory muscle use
- For circulatory status looking for central and peripheral cyanosis, poor capillary refill

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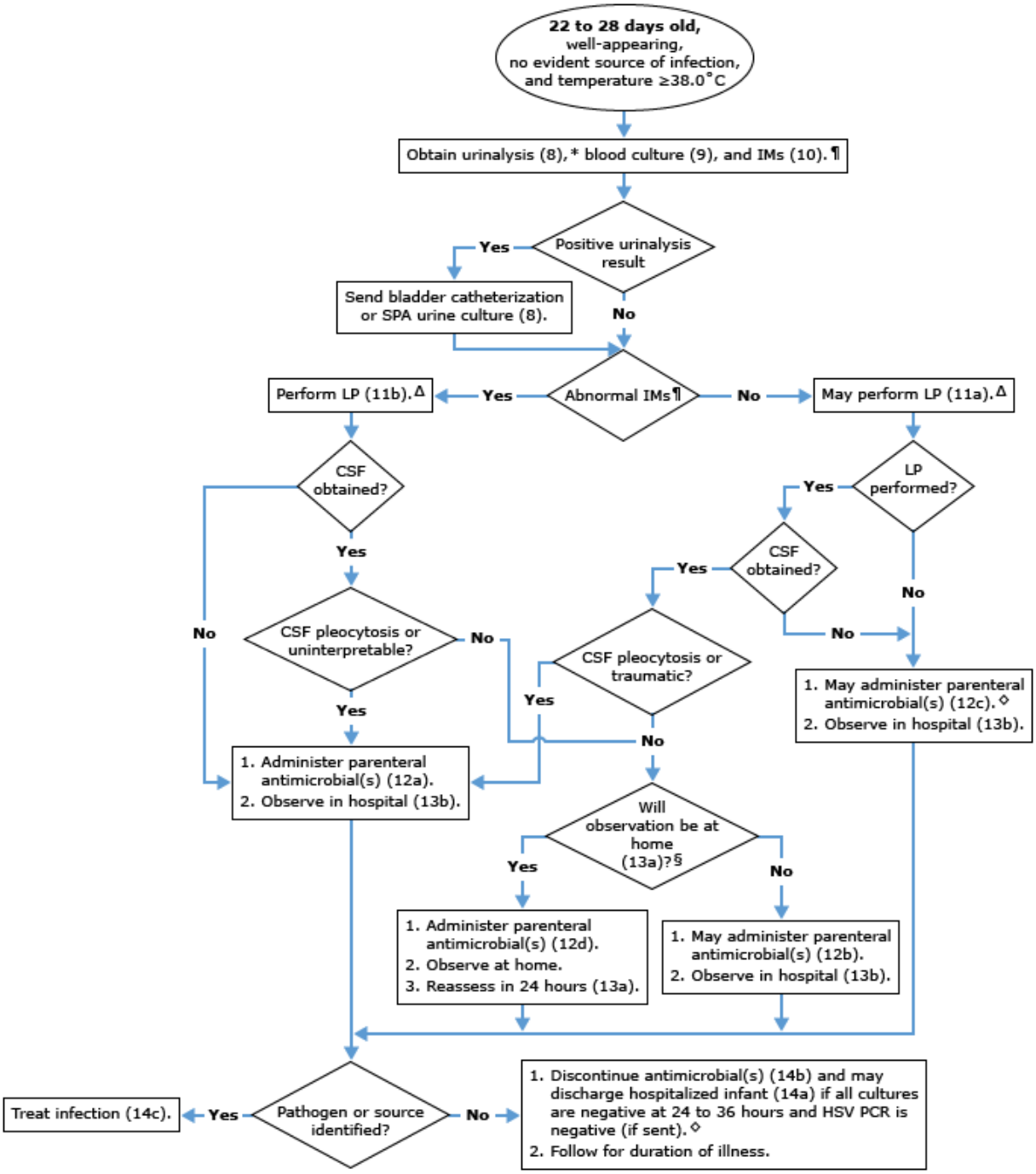
For febrile patients >3 weeks of age with 3/3 PAT the workup has changed regarding need for LP. In these patients you continue to do the workup we talked about but only consider LP if there are elevated inflammatory markers (CRP, WBC) and no other infectious source identified from the initial workup. Regarding management this population still gets empiric antimicrobial therapy and admitted to hospital until culture results are back.



For neonates < 28 days of age who have mucocutaneous vesicles, seizures, CSF pleocytosis with a negative Gram stain, shock/severe ill-appearance, or maternal herpes simplex virus (HSV) infection should receive acylovir empirically.

- IV: 20 mg/kg/dose every 8 hours. Duration dependents on clinical condition, for CNS and disseminated infections at least 21-day, for skin and mucous membrane infections 14-day course

Sources

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Objective 3

In a febrile patient requiring antibiotic therapy, prescribe the appropriate antibiotic(s) according to likely causative organism(s) and local resistance patterns.

Once you've identified an infection, and found a source life becomes simpler, treat with the appropriate antibiotics, Bugs and Drugs, Spectrum and if they're back, gram stain and culture and susceptibilities are your friends.

Objective 2

In a febrile patient with a viral infection, do NOT prescribe antibiotics.

Rapid testing for influenza, covid and other viruses can help determine infectious cause quickly but patients may ask for antibiotics for treatment.

Antibiotics are not effective in infections caused by viruses. Some patients may believe so because they were prescribed them for colds, flus, sinusitis and bronchitis in the past, but it's important to educate patients and let them know they would have gotten better with our without the antibiotics as these illness are most often caused by viral pathogens.
Be mindful of considerations for stewardship and antibiotic resistance

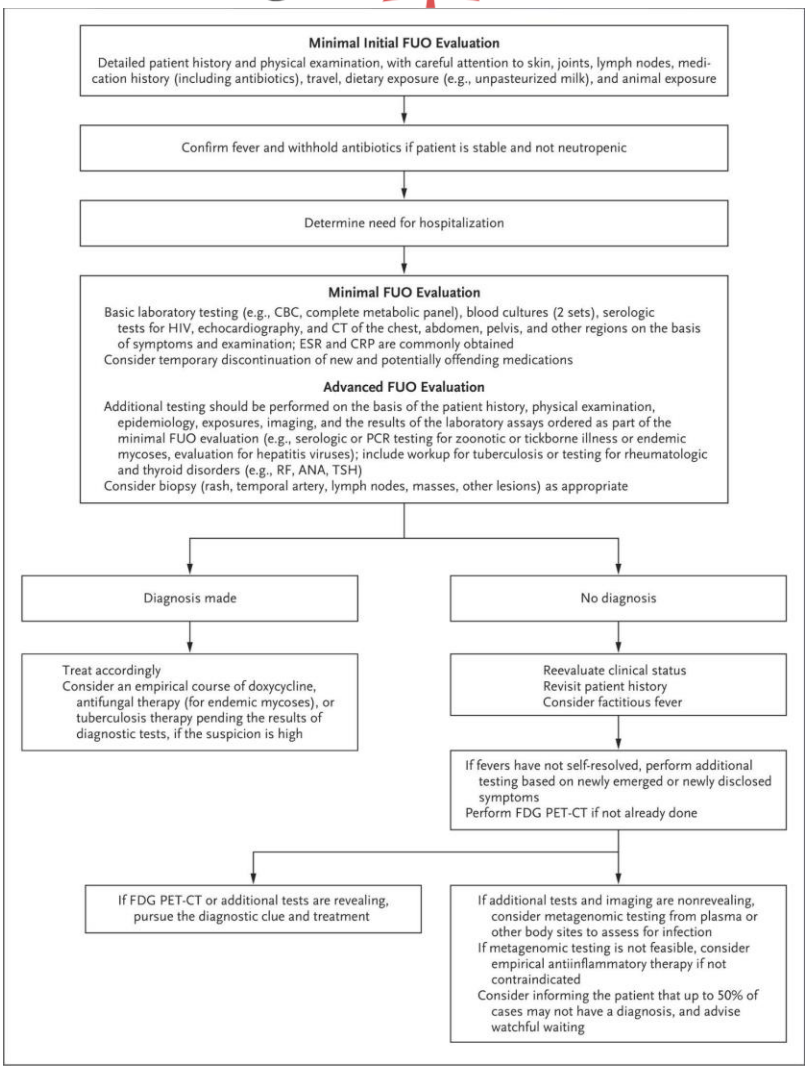
Objective 4

Investigate patients with fever of unknown origin appropriately (e.g., with blood cultures, echocardiography, bone scans).

Fever of unknown origin is defined as a fever for >3 weeks despite 1 week of evaluation.
As the duration of fever increases, the likelihood of an infectious etiology decreases

No Canadian guidelines are apparent for this, but serendipitously, the NEJM published a new article just this month. https://www-nejm-org.ezproxy.lib.ucalgary.ca/doi/10.1056/NEJMra2111003

They have a nice flow chart for the general workup of this patient, which we will include in the shownotes.



The article goes on to relate variable categories of causes over time depending on geography. Roughly half are never solved, around 40% of those diagnosed are infectious, a quarter are autoimmune/inflammatory, and the last quarter being a grab bag.

The categories they suggest including are:

- Infectious, including:
    - bacterial
    - viral
    - fungal
    - others such as vectorborne or zoonotic
- Cancers, most frequently:
    - renal-cell
    - lymphomas
    - hepatocellular
    - ovarian

- Autoinflammatory and Autoimmune
- Drug-associated
    - antibiotics, allopurinol, anticonvulsants, heparin, methyldopa, quinine
    - chemotherapeutic agents
    - vaccines, monoclonal antibodies
    - there is a giant list available in the show notes if you want more
- Nosocomial
    - Surgery associated - which we discuss in the next objective!
    - Neurogenic due to cerebral injury
    - thromboembolic events
    - drugs
- Immunodeficiency Associations
    - HIV infection
        - acute retroviral syndrome ~2 weeks after infection (peak viraemia)
        - of course opportunistic infections
        - Immune reconstitution syndrome can occur if FUO occurs after the initiation of ART
    - Organ-Transplant Recipients

Review surgeries, coagulopathy, medications, recent travel, malignancy, connective tissue disease
Extensive review of systems.

- Fevers can be related to a complication related to the surgery as we'll discuss later
- Coagulopahty, are there risk factors for clotting, fever can be present with: PE, DVT, MI, stroke
- Changing medications and doses can sometimes cause fevers, in the case of malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, and anticholinergic toxidrome, as we'll discuss later
- Recent travel is an important consideration. Patients with fever after tropical travel have malaria until proven otherwise. The classic clinical triad for all species of malaria is fever, splenomegaly, and thrombocytopenia. Also consider Zika, TB.
- Malignancy that sometimes are difficult to diagnose, such as chronic leukemias, lymphomas, renal cell carcinomas, and metastatic cancers, often are found in patients with FUO
- Connective Tissue Disease - rheumatoid arthritis, rheumatic fever, temporal arteritis, IBD, and PMR are common autoimmune sources of FUO because they remain difficult to diagnose even with the help of laboratory testing.

Imaging such as PET-CT to rule out malignancy, inflammatory causes, or covert infection (e.g. osteomyelitis) and CT Head/chest/abdo can help rule out malignancy and abscess

Get specialists involved if needed, such as ID, oncology and rheumatology

Objective 5

In febrile patients, consider life-threatening infectious causes (e.g., endocarditis, meningitis).

They mention two big ones on here.

Endocarditis from Circulation journal 2015
here are the features to look for
Lets keep this simple, we aren't meant to dig too deep into individual diagnoses. It is rare, but deadly, so we don't want to miss it.

Diagnosis is traditionally assessed using the Modified Duke Criteria, this is considered diagnostic if:

- two major criteria are met
- 1 major and 3 minor criteria are met, or
- no major, but 5 minor criteria are met

Major criteria include:

1. Positive blood cultures for typical IE bugs: Strep viridians, HACEK bugs, S Aureus without other site for this bug, or Enterococcus
    a. this needs to be from 2 separate cultures, or two samples more than 12 hours apart, or 3 of 4 cultures with first and last at least 1 hour apart
2. echocardiogram with intracardiac mass on a valve or supporting structures - there is more nuance here as well if you want to read further
3. A single positive blood culture for Coxiella burnetti

Minor Diagnostic Criteria include:

1. predisposing heart condition or IV drug use
2. A temp over 38 deg C
3. Vascular phenomena present, such as:
    a. arterial emboli
    b. pulmonary infarcts
    c. mycotic aneurysms
    d. intracranial bleed
    e. conjunctival haemorrhage
    f. janeway lesions
4. Immunologic phenomena present, including:
    a. glomerulonephritis
    b. osler nodes
    c. roth spots - good luck!

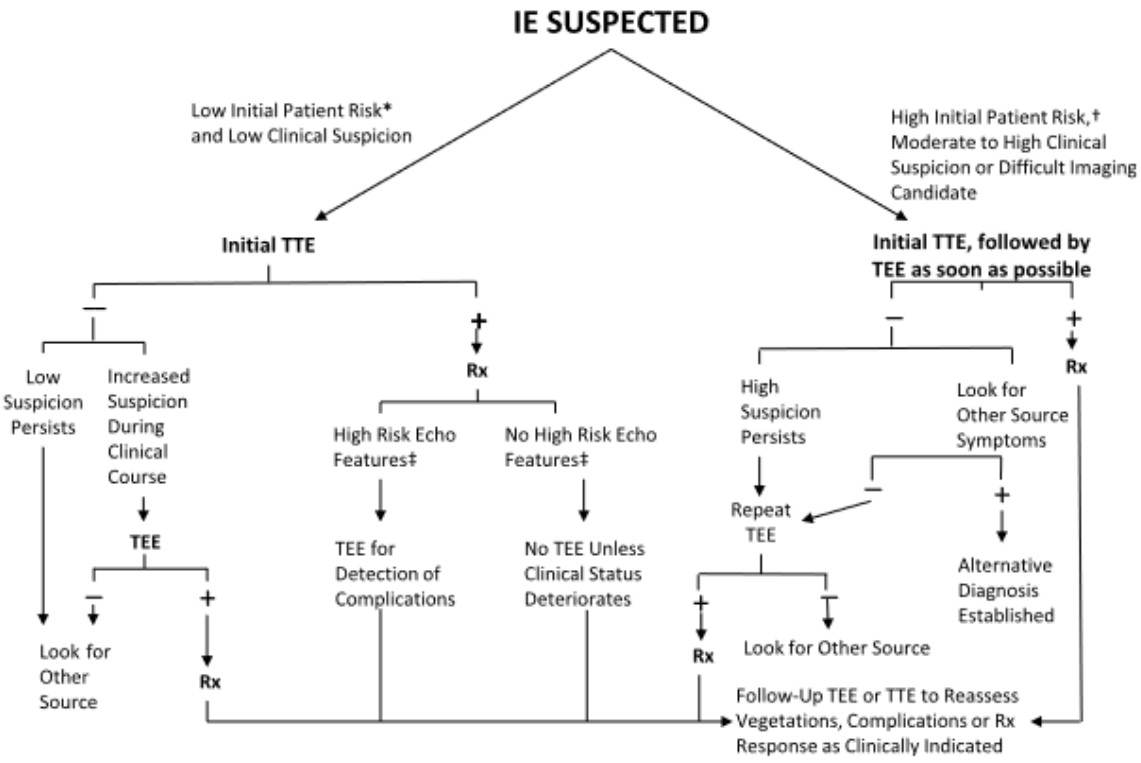
d. rheumatoid factor

5. Microbiological evidence, which means:
    a. positive blood culture but not meeting major criterion

Handy dandy checklist calculator from Merck Manuals
https://www.merckmanuals.com/medical-calculators/EndocarditisMod.htm Canada

That's about it. Have a basic idea of these criteria so if someone comes in with a fever you look for high risk features to rule out this deadly disease.
We've included the approach from the Circulation guidelines to follow if you suspect infective endocarditis.
Essentially, whether high or low suspicion, you should get an initial transthoracic echo, because you can probably get this the quickest. If low clinical suspicion and TTE is negative, you need to go hunting for another source.
If it is high clinical suspicion get a TTE quick, followed by a Transesophageal as soon as is possible. If these are negative, but you still have high suspicion, then get a repeat TEE. If the second one is negative, you need to go hunting for other sources.

Of course in any case if your TTE or TEE is positive, that's a diagnosis and you need to get them on appropriate antibiotics ASAP.



Meningitis CPS 2020 guidelines for children over 2 months of age, and the ESCMID guideline 2016

For the kiddos, the CPS lists the following, not so specific, findings of meningitis:
for infants

- fever
- poor feeding
- lethargy - or decreased interaction with caregivers
- vomiting
- irritability
- +- a rash
- inconsolable crying, prolonged or worsening irritability, or progressing lethargy should flag you further to a CNS focus

nuchal rigidity is noted to be uncommon in infants

older kids
can start to have some more specific findings

- headache
- photophobia
- nuchal pain or rigidity
- impaired consciousness
- as well as the more vague features mentioned for infants

Exam
of course do a full exam if not acutely unwell. Respiratory, and detailed neuro exam.
Neuro should look for:

- focal neuro signs
- posturing
- cranial nerve abnormalities
- level of consciousness

Worth mentioning that the European guidelines relate that “signs and symptoms such as fever, neck stiffness, headache and altered mental status can be absent”, and that “the sensitivity and negative predictive value of Kernig and Brudzinski sign is low in the diagnosis of meningitis and therefore do not contribute to the diagnosis of bacterial meningitis…. and therefore bacterial meningitis should not be rule out solely on the absence of classic symptoms.

Suspicious for meningitis?
You need fluid from the meninges of course, what do we look for on the CSF analysis?

- cell count
- glucose level

- protein levels
- micro culture for bacteria, and viral studies as well

The CPS of course points out that the lumbar puncture should be deferred to get a brain CT first if there is evidence of elevated ICP in the form of: papilloedema, seizure, focal neuro deficits or decreased LoC.

Of course, the antibiotics are critical and so they should not be delayed in the interest of awaiting CT if not immediately available.

Onset of fever after surgery can also provide clues as to the underlying etiology of fever.

If there's a fever after inhaled anesthetic (sevoflorane or desflorane) anesthesia assume malignant hyperthermia. Discontinue the anesthetic, give the patient high flow oxygen + cooling. Give dantrolene.

If fever starts POD 1, it is important to note that atelectasis IS NOT a cause of post-op fever. Inflammatory changes, such as fever or mild elevated WBC are not out of the norm in post op patients. Get a CXR to rule out aspiration pneumonia. Do prophylactic incentive spirometry to prevent the atelectasis from turning into a possible pneumonia

If fever starts POD2, consider pneumonia, can happen when atelectasis isn't resolved. On CXR you will see a consolidation, get blood cultures and treat like hospital acquired pneumonia empirically while you wait for blood culture results

If fever starts POD3, it may be a UTI, UA and UC will reflect that, treat accordingly. To decrease incidence try and remove foley as early as safely possible.

If fever starts POD5, consider DVT/PE, you may see unilateral leg swelling, diagnose with ultrasound. Orthopedic surgeries have the highest risk for DVT/PE. Prophylactic LMWH, early mobilization decreases incidence of DVT/PE

If fever starts POD7, consider wound infection/abscess, look at incision sites, make sure surrounding erythema is resolving. This complication can be mitigated by good closure during surgery and good wound care post-surgery. Wound infections can be treated with antibiotics.

If you're unsure if it's a wound infection VS deep abscess at the surgical site, get an ultrasound. If deep abscess, you need to drain and may need a revision and another surgery.

Objective 7

In the febrile patient, consider causes of hyperthermia other than infection (e.g., heat stroke, drug reaction, malignant neuroleptic syndrome).

As mentioned earlier there are a number of non-infectious cases of fever. We'll outline the management of heat stroke, thyroid storm, neuroleptic malignant syndrome and serotonin syndrome

Heat Stroke

- Consider heat stroke if there has been an temp >40, exposure to heat, altered mental status, and no other diagnosis
- Patient needs rehydration, rapid cooling and. Ice packs in groin and axilla, cool damp sponges/towels/water, fan for cooling. IV rehydration.
- Monitor Labs (CBC, lytes, UA, CK, LFT, Coags)

Thyroid Storm

- When you have a suspicion of hyperthyroidism plus alarm symptoms (fever, delirium, and hypotension)
- B-Blockers (Propranolol 60-80mg PO q4-6h) to slow the heart down and get the BP back up.
- PTU 200mg PO q4h to reduce the production of new thyroid hormone
- Iodine solution (delayed 1h after PTU)
- Iodinated radiocontrast
- High-dose IV hydrocortisone 100mg IV q8h will reduce the T4 to T3 conversion.

Neuroleptic Malignancy Syndrome

- Presents 1-3 days after starting atypical antipsychotic medications.
- Presents with delirium, autonomic instability, fever, and elevated creatinine kinase.
- Treatment is discontinuing antipsychotic medication, and supportive management

Serotonin Syndrome

- Consider if a new serotonergic agent was added or increased in the last 5 weeks.
- Diagnose clinically if on serotonergic agent and one of the following:
    - Spontaneous clonus
    - Inducible clonus PLUS agitation or diaphoresis
    - Ocular clonus PLUS agitation or diaphoresis
    - Tremor PLUS hyperreflexia
    - Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus
- Treat by discontinuing serotonergic agent, supportive management to normalize vitals.

- Consider benzos for sedation, cyproheptadine (antidote) and intubation

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, alert mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis–like rigidity	Hyporeflexia	Agitation

Management

- Stop offending agents
- Supportive care: intravenous fluids and correction of vital signs
- Benzodiazepines
- If temp is more than 41.1 may need ICU level care

Objective 6

Aggressively and immediately treat patients who have fever resulting from serious causes before confirming the diagnosis, whether these are infectious (e.g., febrile neutropenia, septic shock, meningitis) or non-infectious (e.g., heat stroke, drug reaction, malignant neuroleptic syndrome).

We've discussed this in the earlier objectives based on the etiology but it's always helpful to start with the basics of ABCs, Vitals, GCS

Objective 8

In an elderly patient, be aware that no good correlation exists between the presence or absence of fever and the presence or absence of serious pathology.

Signs and symptoms of infection present differently in elderly patients, and it's important to pay attention to symptoms like increased confusion, falling, and anorexia which can be common manifestations of infection, regardless of if patient is febrile.

The general work-up for infections in elderly patients is the same as adult patients. Note that UTI (urinary tract infections) are common in elderly patients and they are at increased risk of infective endocarditis (IE)

If you suspect infection, and empirically treat with antibiotics, they should be discontinued once diagnostic tests are negative.

Thanks again for listening in, and as ever, reach out to us with any feedback and if you want to get involved with the project, we are always looking for awesome people to keep things going and to inject your creativity and awesomeness to make things even better.

Sources

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