Introduction:

Welcome to CUGH's bi-weekly clinical case-series, "Reasoning without Resources," by Prof. Gerald Paccione of the Albert Einstein College of Medicine. These teaching cases are based on Prof. Paccione's decades of teaching experience on the medical wards of Kisoro District Hospital in Uganda. They are designed for those practicing in low resource settings, Medicine and Family Medicine residents, and senior medical students interested in clinical global health. Each case is presented in two parts. First comes a case vignette (presenting symptoms, history, basic lab and physical exam findings) along with 6-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. Two weeks later CUGH will post detailed instructors notes for the case along with a new case vignette. For a more detailed overview to this case-series and the teaching philosophy behind it, see Introduction to "Reasoning without Resources". Comments or question may be sent to Prof. Paccione at: gpaccion@montefiore.org

Note: If you would like to be notified when a new case is posted (along with instructor notes for the previous one), send your e-mail to Jillian Morgan at jmorgan@CUGH.org.

About the Author:

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CASE 39 – Fever and Cough

A 45 year old male presents with 3 days of fever and cough.

He was previously well without prior hospitalizations or known chronic illnesses, working as a Church-school teacher and farmer, always monogamous since marriage, and the father of 5 healthy children 10 to 25 years old. He's never left Kisoro for work.

Three days ago he returned early from the fields feeling weak, "hot and cold", with intermittent chills. He slept uncomfortably, and the next morning was nauseated, vomited twice and had 2 loose bowel movements that then turned watery (without blood) with his 3rd episode. He was too weak to work. The next day he developed a mild dry cough that later became productive of scant white-yellow sputum with streaks of blood. On the day of admission, he awoke confused, talked non-sense to his wife, couldn't get out of bed, complained of abdominal pain and some shortness of breath, and was incontinent of diarrhea. He had no chest pain. His wife became alarmed and called the village health worker who arranged for transport to the hospital.

He never had similar symptoms before, hadn't had unusual problems with abdominal pain, cough or wheezing in the past, doesn't smoke, drinks socially1-2 times/week without becoming drunk, and hasn't lost consciousness, weight, or appetite recently.

Physical Exam:

Sitting up in bed in moderate respiratory distress, occasionally speaking incoherently

BP 78/40 without orthostatic change; HR 156, regular; Temperature, 103.2 axillary; RR 36; pulse oximetry, 88% sat.

Skin: normal, without rash or herpes zoster scar
Eyes: conjunctiva without icterus or pallor;
Mouth: dry mucous membranes; no thrush
ENT: no pharyngeal exudates/erythema; no nasal discharge or sinus tenderness;
Neck: supple, no lymphadenopathy, thyroid palpable/normal; no JVP except when lying flat;
Lungs: dull to percussion and increased tubular breath sounds with I/E ~ 1:2, egophony, and scant crackles over the right lower lung field;
Abdomen: mildly distended, normal bowel sounds, no guarding/rigidity/tenderness or masses noted to superficial or deep palpation; liver span 10 cm to percussion with percussion tenderness noted in RUQ, no edge palpated; spleen non-palpable.

Rectal: soft/watery brown stool, guaiac negative;
Neuro: disoriented to place and time, incoherent, unable to assess attention span; grossly non-focal and moving all extremities; reflexes +2 throughout.

1. What is the "frame" of this case? i.e. the key clinical features the final diagnosis must be consistent with?

- *Previously healthy, no HIV risk factors*
- *3 days of symptoms*
- *Fever >103 axillary*
- *Productive cough with sputum and blood streaks*
- *Shock, and other alarming vital signs: HR >150, RR 36, O2 Sat 88%*
- *Confusion*
- *Focal lung findings with tubular breath sounds, egophony and crackles*

2. a) What is the most likely *organ-specific* diagnosis in this patient, and why?
b) What is the likely explanation for the patient's gastrointestinal symptoms – vomiting, diarrhea and abdominal pain – and the RUQ percussion tenderness on exam?

a) The patient has "community-acquired pneumonia" (CAP) a diagnosis that can be reached from employing either heuristics – pattern recognition of the "classic syndrome" by an experienced physician, or through "Bayesian analysis" of the sequential components of the history and physical.
Bayesian Analysis would proceed like this: the "pretest probability" from the history is high (on the basis of the short duration of illness; and fever and productive cough with blood streaks – which imply invasive inflammation; and the confusion and GI symptoms which are signs of sepsis and a serious deep-seated bacterial process); if we consider the "test" in this case the physical exam, a few of the findings in this patient's lung exam are each over 95% specific for pneumonia (i.e. tubular breath sounds and egophony) - with tachypnea, crackles and percussion dullness contributing to a "composite" specificity of over 99% and likelihood ratio >200. When integrated with the high pretest probability, the post-test probability for CAP approaches 100%: i.e. there's no doubt about this one.

b) The final cognitive steps of rational diagnosis involve reviewing the candidate disease for its comprehensive yet "parsimonious" explanation of symptoms, and its coherency, i.e. does it all "make sense" patho-physiologically and epidemiologically.
These final criteria for reaching a sound diagnosis are met in this patient by "CAP": "shock and other alarming vital signs" are indications of the severity of the process and one of its dreaded complications – septic shock; and the confusion and GI symptoms are manifestations of the "sepsis syndrome" mediated by cytokines that both induce delirium and stimulate the GI tract - vomiting and diarrhea.
Pneumonias, particularly basilar pneumonias commonly cause referred pain in the abdomen, and RUQ percussion over the liver may be jarring the inflamed parietal pleura. (N.B. Non-specific RUQ pain on percussion is common in my experience even when no plausible

explanation is apparent – an observation initially tested and corroborated by many (unnecessary) negative ultrasounds.)

3. a) What are the usual *clinical* features (i.e. from the history and physical exam) of this disease in adults and children?
b) What is their diagnostic accuracy (likelihood ratios, and/or sensitivity/specificity) from studies in *developed* countries?
c) How would these parameters likely change if assessed in African cohorts with this disease?

a) CAP usually presents with a history of some combination of acute cough, fever (80%), chills (40-50%), rigors (15%), chest pain (30%) (Marrie TJ. Community-acquired pneumonia. Clin Infect Dis 1994; 18:501); after a mean of 2-4 days for bacterial and legionella pneumonias, 10-14 days for mycoplasma pneumonia.
Cough may not be present initially since the alveoli have few cough receptors. Cough begins when the infection irritates cough receptors in the airways. Weakness and lethargy are seen in the vast majority of patients at presentation. Delirium and GI symptoms are common and a sign of increased severity of disease. In the elderly, fever is often absent; tachypnea (45-70%) and tachycardia may be the most sensitive signs of PNA in the elderly (UpToDate, Diagnostic approach to community-acquired pneumonia in adults, Bartlett, J.G.).

On exam at presentation in adults: 30-70% have fever, 40% a RR>28, 20-60% HR>100; (N.B. fever alone increases respiratory rate: in children without pneumonia, the RR can increase 10 breaths per minute per degree Celsius.).
Findings on lung exam include percussion dullness, diminished or increased-bronchial/tubular breath sounds, egophony, and crackles.

b) The utility of the lung exam is plagued by only fair-moderate inter-observer agreement for many signs (e.g. with kappas between 0.3-.55 for percussion dullness, decreased breath sounds, crackles, bronchial breathing, wheezes); and lower for some, e.g. whispered pectoriloquy, 0.11.

The accuracy of the exam (i.e. sensitivity, specificity, likelihood ratios) is highly variable between studies – a reflection of variability in entry criteria, severities of illness, and skills of examiners between the studies. Thus crackles are reported in ~20-70% of patients with PNA (sensitivity), but also in 5-60% without PNA (specificity of ~40-95%). These data produce a LR+ of 1.8 and LR– of 0.8 – seemingly not very helpful diagnostically. For signs of consolidated lung (dullness, bronchial breath sounds, egophony), the sensitivities are lower (~5-20%) but their specificities are high (>90%) and their LRs+ in the 3-4 range.

Although reviews of the literature often conclude from these numbers that the history and exam have little to offer diagnostically, in many clinical situations the history and physical are all you need to rule in or rule out PNA with an accuracy sufficient to guide therapy.

- *the diagnostic standard in most studies was the chest x-ray (CXR) which itself is imperfect: many PNAs don't show up on CXR but do on CT; and viral infiltrates on CXR*

do not respond to antibiotics but are indistinguishable from bacterial infiltrates which do. (See below, #5)

- *clinicians rarely consider exam findings in isolation, but rather "put them together" in arriving at diagnoses – as does Bayesian analysis. For example, unimpressive LRs of 2-4, when multiplied together a few times result in "composite LRs" of 8-60. (Creating "composite LRs" of procedurally-independent findings is a major mathematical advantage of using LRs instead of sensitivity/specificity). Thus an acutely tachypneic, febrile patient with percussion dullness, crackles, and bronchial breath sounds has a composite LR+ for PNA (multiplying only 3 of the LRs together) of ~20 – enough to raise a pretest probability of 5% to a post-test probability of ~50%, or one of 10% to ~70% - which in most clinical settings justifies antibiotic therapy. (If a CXR was negative, most wise clinicians would still treat with antibiotics and repeat the CXR in 24-48 hours, and/or with clinical improvement noted, finish the course of therapy.) N.B. Because of some redundancy or lack of complete "independence" among most tests/signs, sequential multiplication beyond 3 LRs can lead to an inflated composite LR. However, any additional positive findings certainly add to the probability of the diagnosis.*
- *Heckerling, et.al (see suggested readings) derived and validated a clinical prediction rule for infiltrates on CXR in which 0-1 finding had an LR of 0.3, and 4-5 findings an LR 8.2. The 5 findings were temperature >37.8, HR > 100, crackles, diminished breath sounds, and absence of asthma.*

c) The published sensitivity of the history and physical exam, determined in patients living in developed countries, is probably too low to apply in practice in Africa. African patients without access to care present later in the course of disease and the PNAs that come to medical attention are likely to be the more serious ones. Thus, symptoms are more likely to be present and serious; and exam findings to be multiple, advanced and classic (e.g. bronchial breath sounds and egophony are later manifestations of PNA, appearing 2-3 days after hospitalization in the pre-antibiotic era, probably 5-7 days post-symptom onset. Thus they are rarely heard in U.S. patients with PNA who present to medical attention well before that). Thus the sensitivity of signs and symptoms in African patients with PNA is higher.

Specificity of these same findings however may be lower: the burden of pulmonary disease is higher in Africa, much of it untreated. Scars from prior pneumonias and/or tuberculosis leave crackles and other signs in their wake, likely leading to more "false positives" in acutely febrile patients without CAP.

Although the lower specificity of the exam findings in Africa lowers their diagnostic predictive value, this is probably more than offset by the higher prevalence of PNA in African patients who present with respiratory symptoms and/or fever - estimated to be at least 5 times higher. Pneumonia is simply more likely to be present in under-nourished populations with a high disease burden and prevalence of HIV. In Bayesian terms, the higher prevalence of disease means "pretest probability" is higher in the individual patient and even imperfect physical findings in the right clinical context are more likely to reflect pneumonia than they are in the

U.S. Similarly, in Africa, CPRs for acute infiltrates such as Heckerling's are likely to reflect a higher probability of PNA at each numerical cutoff.

4. a) What organisms cause this disease in adults and children?
b) What clinical features suggest a higher likelihood of (which) specific microorganisms, and how predictive are they?
c) Can you apply them to this patient?

a) Almost any pathogen can affect the lungs - including organisms rarely encountered such as leptospirosis, typhus, Q fever, endemic fungi, etc.
- However, although specific pathogens are identified in only 5-20% of CAP, in developed and probably most developing countries, the majority of cases of CAP are caused by pneumococcus (40-60% of identified pathogens), H.influenzae and atypical pathogens such as mycoplasma, chlamydia and legionella.
- The major exception in developing countries like Uganda is tuberculosis, one of the principal pathogens in most series of hospitalized patients.
- Viruses cause up to 20% of cases of CAP, either as the sole pathogen or as a co-pathogen complicated by a bacterial pneumonia – particularly influenza and parainfluenza, but also adenovirus, respiratory syncytial virus and human metapneumovirus.
- Although pneumococcus is the most frequent post-viral pathogen, S. Aureus is second.
- Most cases of S. Aureus pneumonia occur in either debilitated hosts or as post-viral super-infections.
- Gram negative bacteria like Klebsiella are considerations in alcoholics and patients with pre-existing lung disease;
- Anaerobic infections are predominantly seen in patients at risk of losing consciousness and aspirating (e.g. epileptics, alcoholics).
- CAP is an AIDS-defining illness and often the initial manifestation of underlying HIV-infection. HIV increases the likelihood of pyogenic bacteria and TB as causes of PNA as "atypicals" are not seen more frequently in HIV infected hosts, but PCP must be considered in patients with CD4 counts below 200.

b) Clinical features can suggest certain pathogens, but in general are non-specific.

- *Rapid progression and shock in a previously healthy adult or child, particularly when associated with hemoptysis, suggests necrotizing pneumonia. Necrotizing PNAs can be caused by a few organisms: particularly virulent strains of pneumococcus (especially serotype 3 and 19); methicillin resistant S. Aureus (MRSA) strains that bear genes for the Panton-Valentine leukocidin (PVL); Klebsiella; Group A Streptococcus; Legionella; and some anaerobic infections post-aspiration.*
- *Indolent progression of symptoms and/or cough over weeks to months, suggests tuberculosis or abscess. Constitutional symptoms are usually present, fever may only be registered symptomatically as "sweats", and dyspnea is infrequent in uncomplicated infections.*
- *Progression over weeks in an AIDS patient, particularly when associated with dyspnea, suggests PCP (especially if non-adherent to TMP-SMX prophylaxis).*

- *Dry cough, indolent progression over 1-2 weeks, upper respiratory symptoms and/or wheezing on exam suggest viral or mycoplasma infections. Wheezing lowers the probability of both a pneumonic infiltrate on CXR and a bacterial infection.*
- *Viral PNA is more common in children especially infants, although well-recognized in adults. According to the British Thoracic Society, in kids bacteria tend to cause higher fevers (>38.5C), faster respiratory rates (>50/min) and chest recession, whereas viruses cause more striking chest recession and wheezing and occur at a younger age (Lancet 2011; 377:1264).*
- *Dyspnea developing over many days to weeks associated with non-productive cough (without evidence of massive pleural effusion on exam) suggests interstitial pathology – seen with viral PNA, PCP and hypersensitivity pneumonias (which are uncommon-rare in most settings). N.B. Dsypnea and dry cough could also be caused by CHF, and a recent fever and/or sputum by a complicating bacterial PNA.*
- *Diabetes, underlying lung disease caused by indoor smoke inhalation, old TB, etc., are associated with a higher prevalence of gram negative infections (Klebsiella, Pseudomonas, Moraxella catarrhalis, E.Coli) and S. Aureus.*
- *An acute presentation over 1-4 days with evidence of focal consolidation on lung exam suggests pneumococcal pneumonia, as does "rust-colored sputum".*
- *A previous viral syndrome followed by acutely worsening respiratory distress, spiking fevers and/or sputum production suggests a bacterial super-infection – usually by pneumococcus, S. Aureus or group A strep.*

c) Our patient was previously healthy, has no suggestions of underlying HIV disease, and is now acutely and critically ill, in shock with blood-streaked sputum…. a clinical picture consistent with severe necrotizing pneumonia.

5. In patients with this illness, how reproducible and accurate is radiologic imaging (i.e. imaging that *might* be available in rural Africa) for making a) the organ-specific diagnosis and b) identifying the organism?

In rural Africa, the only radiologic imaging that's occasionally available in district hospitals is a chest x-ray.

Studies on inter-observer variability of diagnosing PNA by CXR have demonstrated an observed agreement between radiologists above 80% but only a moderate "kappa" (a measure which adjusts for chance agreement) of ~.5. However, the observed agreement is lower, only 59%, in CXRs with positive findings (while above 90% if the CXR is normal). Underlying lung disease makes agreement even harder to achieve: the kappa is only fair (~.2) in patients with COPD (see Hopstaken).

Vis-à-vis accuracy, when CXR is compared to high-resolution CT scans, it misses about 30% of pneumonias (sensitivity 70%) and their presence bilaterally in 60% . Although it's controversial, dehydration is thought to be a reason for falsely negative CXRs initially… which then "blossom" with infiltrates a day or 2 after hydration. (Although in dehydrated patients more infiltrates

indeed appear after hydration, many think that's because the pneumonia is evolving over time and hydration plays little role in its appearance.)

CXR can't differentiate between bacterial and viral causes of CAP. Traditionally, alveolar infiltrates have been considered to be bacterial and interstitial infiltrates, viral. However in a study of 254 children with CXR-defined PNAs in whom 215 had a specific etiology determined, the sensitivity and specificity of alveolar infiltrates for bacterial pneumonia were 72 and 51%, respectively; and the sensitivity and specificity of interstitial infiltrates for viral pneumonia were 49 and 72% (UpToDate, Clinical Features and Diagnosis of CAP in Children; Thorax 2002; 57:438).
Lobar infiltrates with exam signs of consolidation are very suggestive of bacterial pneumonia but are infrequent (<5% of all PNAs). Most commonly caused by pneumococcus, other prominent causes of lobar pneumonias are tuberculosis (common in Africa) and Legionella (often multi-lobar, but rare).

Ultrasound has been investigated as a diagnostic test for PNA as well and has shown promise - in the right (trained) hands operating the right equipment. (European Journal of Internal Medicine 23 (2012) 391–397), but such capacity isn't widely available at present in rural Africa.

6. a) Which tests should be ordered in rural Africa for this illness, and how does your recommendation differ for patients in the U.S.?
b) Describe briefly the accuracy and/or utility of non-radiologic non-invasive diagnostic tests available in the U.S., and in Africa.

a) In general in Africa, the following tests should be performed routinely when CAP is considered:

- *pulse oximetry – readily available in most settings, the "pulse ox" can corroborate or call into question the diagnosis of PNA, and help assess severity;*
- *AFB smear for TB. In HIV negative patients with an acute (days) illness that fits CAP closely, AFB smears may be withheld pending treatment response, but in most cases one should have a low threshold to do this non-invasive test for TB, one of the 2 most prevalent pneumonias in Uganda.*
- *HIV test in patients without a prior recent result.*

In the U.S. when PNA is a consideration, CXRs are considered routine, indeed necessary given the limitations of clinical exam. However, as discussed above, the CXR itself is an imperfect test; in many patients the clinical exam is sufficient for diagnosis of CAP (in those with classic, highly specific findings) and/or therapeutic decisions regarding antibiotics and fluids; and ultimately treatment is more germane to acute patient management than diagnosis per se.

CXRs should be performed on admission in Africa if the diagnosis is uncertain, a complication such as a large pleural effusion or abscess is suspected, or when the results might change therapy (e.g. necrotizing pneumonia). Clinical progression of disease being treated is a reason to order a CXR post-admission.

b) Potential microbiologic tests for CAP include gram stain, culture of sputum, culture of blood, and urinary antigen detection for pneumococcus and Legionella. Only the first 2 are available in rural Africa. However in one large prospective study (van der Eerden MM, et al. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2005; 24:241) complete evaluation that included bronchoscopy when sputum wasn't available only identified pathogens in 60% of patients; adequate sputum was obtained in only 17%, and urinary pneumococcal antigen was 54% sensitive in patients with pneumococcal PNA. In other studies urinary pneumococcal antigen varied between 60 and 80% depending on the severity of disease, higher with bacteremia, lower with sputum culture/gram stain diagnosis. Although "adequate" may be infrequent, when such sputum samples are obtained (defined as <10 epithelial cells and >25 PMNs under low power (x 100)), gram stain identifies the pathogen >80% of the time.
Sputum cultures, when pneumococcus or H. influenza is the etiologic agent, are often falsely negative because of their fastidious growth requirements.
Blood cultures are positive in 10-20% of patients (and false positive blood cultures are almost as frequent).
In the U.S., review of Medicare data showed that only 7.6% of patients hospitalized with CAP had a pathogen detected (Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis 2011; 52 Suppl 4:S296.)

7. a) Clinically relevant *predictive indexes* have been published for this disease: what questions do they address?
b) When you apply these indexes to this patient, what do they predict?

a) Developing "Clinical Prediction Rules" (CPRs) for CAP has been an active area of high-quality clinical investigation.

Published CPRs address the following questions relevant to our patient:

- *Does a patient with respiratory symptoms have pneumonia (an infiltrate on CXR)?*
- *Is a patient with CAP bacteremic (positive blood cultures)?*
- *What is the prognosis (risk of mortality) in a patient with CAP?*

b)
Does this patient with respiratory symptoms have pneumonia (an infiltrate on CXR)?
Heckerling, et.al derived a CPR for CXR infiltrates in Illinois and validated it in 2 other states. The CPR assigned one point for each of 5 variables - Temp >37.8 C; pulse >100 beats/min; rales; decreased breath sounds, absence of asthma: 0-1 points were associated with <10% probability of infiltrate and an LR of 0.3; 4-5 points, with probabilities >50% and LR 8.2. (Of note, ~20% with wheezing on exam had PNA so wheezing doesn't "rule out" PNA; dullness to percussion, egophony, and bronchial breathing were other signs strongly predictive of PNA but too infrequent to enter the "clinical-statistical creation" of the CPR.)

Applied to our patient: 1 for fever, pulse, rales, absence of asthma = 4 points; plus a bonus point for egophony/bronchial breath sounds and dullness (not included in the CPR but even more specific for PNA) = 5 points.

Is this patient with CAP bacteremic (positive blood cultures)?
Falguera, et.al derived and validated a CPR to predict bacteremia in patients with CXR-defined CAP in immune-competent hosts from retrospective analysis of data bases from 2 Spanish university hospitals. The CPR was based on 6 variables, each assigned a point: chronic liver disease, pleuritic pain, HR>125, RR>30, SBP<90, and absence of prior antibiotic treatment. In 3 cohorts (1 derivation, 1 internal validation, and 1 external validation) a score </= 1 carried <8% risk of bacteremia, whereas a score of 2-3 carried a 14-27% risk and >/=4 a >/=30-63% risk
Applied to our patient: 1 for HR, RR, SBP, and absence of prior antibiotics, or ~30% risk of bacteremia.

What is the prognosis (risk of mortality) in a patient with CAP?
The Pneumonia Severity Index, which meets the highest quality standards for CPRs, was derived and broadly validated to identify CAP patients at low risk for mortality within 30 days of presentation. Its 20 variables are based on history, physical exam and labs easily available at presentation in hospitals in the U.S.
The PSI is applied in 2 steps: In Step 1, 11 variables are used to identify the lowest risk "Class I" patients by the absence of all of the following: age >50; co-morbid disease – cancer, CHF, stroke, renal or liver disease; and Physical Exam – altered mental status, HR >125, RR > 30; SBP < 90; temperature <35 or >/=40. If ONE or more are present, the patient is not in Class I (0.1% mortality), and a more complicated scoring system is used to divide patients into 4 more Classes of risk from 0.6% mortality in Class II, to 9.3% Class IV, and 27% Class V.
For these classes different points were assigned for test values: BUN, hematocrit, glucose, arterial pH and pO2, sodium, and pleural effusion on CXR. Requiring these lab values makes the PSI difficult to apply in rural Africa.

The CURB-65 score, based on 5 easily measured factors, is much simpler than the PSI: confusion, urea (BUN), respiratory rate >30, BP (SBP<90, DBP<60), and age >/=65. Scores of <2 are associated with mortality rates of <2%, whereas 4-5 with a 40% mortality.

The CRB-65 omits the BUN while maintaining good predictive power, and thus is most applicable to rural Africa. In a study in Germany, patients with scores of 1-2 had <5% mortality, and 3-4, 20-25% mortality.

Other indexes exist to predict need for ICU care in the West. In general, predictive factors include low SBP, hypoxia, multilobar PNA, hypoalbuminemia, acidosis, tachypnea, tachycardia and confusion.

Our Kisoro patient couldn't have lab tests nor an admission CXR. However, simply based on age and physical exam findings his PSI already reaches 125 – the cutoff for Class V being 130 with a mortality >25% .

The CRB-65 scores 3 points, associated with 20-25% mortality.

N.B. In Africa, with a higher burden of disease, more malnutrition, and far fewer hospital resources, the mortality rates at all classes or CPR scores are likely to be higher.

8. a) What principles guide the *treatment* of patients with this disease?
b) How would you treat this patient? [N.B. his HIV test was negative]
c) What response should you expect, over what period of time and what clinical features determine that response?
d) What should be considered if the patient is still febrile (e.g. >100.5) after a week of treatment?

a) Given the inaccuracy of available tests for the microbiologic diagnosis of PNA, and studies showing empiric therapy to be as effective as microbiologically targeted therapy, treatment of CAP is EMPIRIC.

Therapy is directed at the most likely and/or most aggressive pathogens which vary by:
- *environmental exposure and geography;*
- *patient co-morbidities (e.g. pre-existing lung disease);*
- *severity of illness (severely ill patients are more likely to have legionella, MRSA, Klebsiella and other gram (-) bacteria and influenza); and*
- *risk factors for harboring resistant organisms (e.g. for drug-resistant S. pneumonia in adults, risk factors include age >65, antibiotic therapy within the past 3-6 months, alcoholism, medical comorbidities and immunosuppressive illness or therapy). [See File, T.M. Treatment of community-acquired pneumonia in adults who require hospitalization UpToDate]).*

In general, the sicker the patient, the broader the coverage with multiple and usually progressively more expensive antibiotics to which fewer organisms are resistant.

Therapy should also take into account local resistance patterns. In rural Uganda there are NO microbiology-culture facilities in rural areas, but of particular relevance, in a study from 2001 from Mulago Hospital in the capital Kampala, penicillin-resistance was found in >95% of S.pneumoniae isolates (!). Nevertheless, almost all patients with penicillin-resistant pneumococcus or beta-lactamase producing H. influenza could be successfully treated with parenteral ampicillin followed by oral amoxicillin. Despite this "antibiotic discordance" the tissue levels of ampicillin appeared to be higher than the MIC levels of ampicillin against these organisms in most CAP cases. (Am. J. Trop. Med. Hyg., 64(3, 4), 2001, pp. 172–177)

b) Our patient, despite his relative youth and lack of co-morbid illness, is severely ill. The disease process is aggressive, with shock, and probable bacteremia and pulmonary necrosis. Initial antibiotics should cover particularly virulent strains of pneumococcus (by far the most likely pathogen); methicillin resistant S. Aureus (MRSA) strains; Group A Streptococcus; and

probably Legionella and gram (-)'s like Klebsiella (the latter, not because they are likely pathogens but because if missed by the initial antibiotics, will likely prove lethal).

The British Thoracic Society has guidelines that advocate antibiotics that are "older" than those recommended by the IDSA/ATS in the U.S - antibiotics that are thus more likely to be available and affordable in Africa.
In this severely ill patient, BTS guidelines recommend amoxicillin-clavulanate potassium 1.2 grams IV three times daily plus clarithromycin 500 mg IV twice daily; OR Cefuroxime 1.5 grams IV three times daily or cefotaxime 1 gram IV three times daily or ceftriaxone 2 grams IV once daily, plus clarithromycin 500 mg IV twice daily.
If clarithromycin isn't available, azithromycin or doxycycline can substitute, preferably parenteral.
To cover community-acquired MRSA/MSSA, to the above regimen, TMP-SMX or clindamycin should be added.
In many district hospitals, even many of the above "older" antibiotics aren't available. In that case, a "kitchen sink" of whatever is available that will cover the above pathogens is appropriate: e.g. high dose ampicillin IV, TMP-SMX or clindamycin, an aminoglycoside (gentamycin).

How to later pare down broad anti-biotic coverage without culture or antigen testing is challenging. Ideally, a good sputum gram stain obtained on admission before antibiotics can help guide therapy later: if a single gram negative rod or gram positive cocci that look like Staph are seen, treatment should continue to cover gram negatives and Staph as above (and if gram (-)'s are seen, add an aminoglycoside).
If gram stain on good sputum can't be done or doesn't show Staph or gram (-)'s, after stabilization, finishing the course with high dose oral amoxicillin and doxycycline is reasonable, monitoring carefully for deterioration.

c) When using empiric therapy as a diagnostic test, time to improvement and cure is critical in decision-making.
With most patients with CAP, improvement is noted within 2 days and stabilization of vital signs (afebrile, HR <100, RR <24, SBP >90, O2 saturation>90%) within 3-4 days.

Quoting an article from Halm, et. al (Time to Clinical Stability in Patients Hospitalized With Community-Acquired Pneumonia: Implications for Practice Guidelines JAMA. 1998;279 (18):1452-1457),

"Among the 385 patients with HRs of more than 100 beats/min on admission, the median time to stabilization (HR ≤100 beats/min) was 2 days. Among the 7% patients with SBP lower than 90 mm Hg on presentation, the median time to stablize (SBP ≥90 mm Hg) was also 2 days. Similarly, among patients admitted with abnormalities in RR, oxygen saturation, and temperature, the median time to stablize RR (≤24 breaths/min), oxygen saturation (≥90%), and temperature (≤37.2°C [99°F]) was 3 days. By day 4, over 75% of all HR, SBP, and RR abnormalities had been resolved. The time course of resolution of fever depended on the criterion for stable temperature. Over 75% of patients admitted with a fever had a stable temperature by day 3, when stability was defined as maximal temperature of the day of 38.3°C or less (101°F). However, according to the most conservative definition (highest temperature of the day ≤37.2°C [99°F]), stability was not reached by 75% of patients until day 6. Among the 8% of patients who were admitted with an acute change in mental status, the median time to return to baseline mental status was 3 days. Among patients who were unable to eat on admission (or were ordered not to eat by their physicians), the median

time to being able to eat was 2 days. The time to stability of other functional status measures was also rapid (stable bladder and bowel function: median, 1 day; abililty to ambulate: median, 2 days)."
This study also found that time to stability was longer for patients who were sicker (by PSI), with a median time to defervesce below 99F of about <u>one week</u> in PSI Class IV-V (our patient's Class).

Other studies are consistent with the above: a study from Spain in patients with more co-morbid disease found a median time to vital sign stability of 4 days (Menendez R, et.al. Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. Clin Infect Dis 2004; 39:1783–90). *This study also identified 6 independent variables recorded during the first 24 hours after hospital admission related to the time needed to reach stability: dyspnea (hazard ratio [HR], 0.76), confusion (HR, 0.66), pleural effusion (HR, 0.67), multilobed CAP (HR, 0.72), high pneumonia severity index (HR, 0.73), and adherence to the Spanish guidelines for treatment of CAP (HR,1.22).*

Of note, cough and crackles take more time to resolve – up to weeks in many patients.

Our patient was short of breath, confused, and had a high severity index based on clinical features alone. Thus, we should expect full stability to take longer than the usual 3-4 days; fever to decline in the first 2-3 days but not get to below 101 for 4-5 days.

d) Lack of response to treatment after 72 hours can be due to either persistent or progressive pneumonia.

<u>Persistent</u> pneumonia is usually related to patient-related factors such as severity of illness and co-morbid diseases;

<u>Progressive</u> pneumonia implies clinical deterioration and suggests drug-resistant organisms, unexpected/untreated pathogens (like TB or anaerobes in this case), an infectious complication of PNA like empyema or abscess, superimposed infection, post-obstructive PNA from masses or nodes. Non-infectious causes of the initial infiltrate have to be considered as well, like malignancy or bronchiolitis obliterans organizing pneumonia; or of the fever e.g. drug fever, other infections such as HIV, etc.

Understanding the natural history of treatment response in CAP is essential in answering the queston "What should be considered if the patient is still febrile (e.g. >100.5) after a week of treatment?". In most cases, and especially with our patient, the most likely reason would be a high severity of illness: a quarter of patients with Class IV-V PSI (or its equivalent) take over a week to get to a temperature below 101F and 2 weeks to fully resolve abnormal vital signs. However, the question of "fever" can't be addressed in isolation but rather must take into account overall clinical status: is the patient eating, feeling stronger, walking? Is the physical exam improving or getting worse? Is the fever trending up or down?

The patient described in the vignette showed clear signs of improvement with fluids and antibiotics after 24 hours which continued. He was still febrile on day 5 to 101, but the fever trend was down-sloping, his confusion cleared in 2 days, and his exam didn't progress. He left the hospital after a week.

Suggested Readings*: (in addition to references in text)*

UpToDate (this internet-based reference has an excellent series of articles on pneumonia in adults and children)
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Metlay, J.P. et al Does This Patient Have Community-Acquired Pneumonia? Diagnosing Pneumonia by History and Physical Examination JAMA. 1997;278:1440-1445
McGee, Steven, *Evidence Based Physical Diagnosis* 2nd Edition, 2007, Saunders/Elsevier