Fever of Unknown Origin or Fever of Too Many Origins?

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Perspective
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Petersdorf and Beeson’s classic articles cataloguing the causes of fever of unknown origin (FUO) have framed the way generations of physicians think about fevers whose source is not readily explainable.¹ FUO as they define it — a temperature rising above 38.3°C (101°F) on several occasions over a period of more than 3 weeks, for which no diagnosis has been reached despite 1 week of inpatient investigation — is considered classic FUO. In the past 60 years, clinician-scientists have tracked the changing causes of these problematic fevers, as disease patterns and definitions have changed and as improved serologic and imaging technologies have begun revealing diagnoses more quickly. The standard definition of FUO no longer includes the requirement for a week of inpatient evaluation. And in the early 1990s, Durack and Street proposed dividing FUOs into four groups: classic, nosocomial, neutropenic, and HIV-associated.²

According to Petersdorf and Beeson’s original report, FUOs were caused by infection (in 36% of patients), malignancy (19%), collagen vascular diseases (19%), and miscellaneous other causes (19%), such as drug fever.³ No cause was determined in 7% of patients. It is paradoxical that despite the introduction of computed tomography (CT), magnetic resonance imaging, improved culture techniques, numerous new serologic assays, and polymerase-chain-reaction studies, in recent years more FUOs have actually eluded diagnosis. In 2003, Vander schueren and colleagues reported that in nearly a third of 290 immunocompetent patients in Belgium, no diagnosis was made,³ and in 2007, Bleecker-Rovers et al. reported that among 73 immunocompetent patients from five hospitals in the Netherlands, no cause of FUO was identified in 51% of cases.⁴

As an infectious-disease physician who has practiced at academic, tertiary care facilities in the metropolitan New York area for nearly three decades, I’ve been struck by the fact that traditionally caused FUOs are now rarer than the FUOs that I’m increasingly asked to evaluate. The new FUOs are often found in patients in the intensive care unit (ICU) who have traumatic brain injury, other neurologic events, or dementia; are mechanically ventilated; have some combination of urethral, central, and peripheral catheters placed; have recently undergone surgery; and are already receiving multiple broad-spectrum antibiotics. However, they continue to spike multiple fevers daily for weeks and sometimes months on end, usually without other signs or symptoms of sepsis.

Physical examination often reveals edema (if not anasarca), early decubital ulcers in the sacral region at minimum, cutaneous eruptions that do not appear to be drug-related, mild abdominal distention, wounds that
have minimal erythema and some serous drainage without purulence or obvious infection, no signs suggestive of deep venous thrombosis, and coarse breath sounds on respiratory exam. And their lines have been recently changed.

Laboratory results include normal or mildly elevated white-cell counts; intermittent coagulase-negative, staphylococcus-positive blood cultures; urinalysis with intermittent pyuria and cultures revealing, sequentially, various gram-negative organisms with counts of 10,000 to 20,000 colony-forming units interspersed with negative cultures; sputum samples with few or moderate numbers of white cells; and chest images revealing bilateral basilar congestion with atelectasis, whose readers say they cannot rule out infection. Wound cultures reveal several bacteria but few, if any, white cells, and CT scans show “postsurgical” changes or small fluid collections not particularly suspicious for infection. Sinus films invariably demonstrate thickened sinus membranes without air–fluid levels or other clear-cut findings of sinusitis. Venous Doppler studies are negative or reveal nonocclusive thrombosis. C-reactive protein (CRP) levels fluctuate wildy from day to day. Clostridium difficile assays performed because of chronic loose stools are invariably negative. The transthoracic echocardiogram is normal, and there is a debate about the safety of and need for a transesophageal echocardiographic study.

Generally, before I evaluate the patient, many diagnostic studies have been done. Nevertheless, determining the cause of a fever and which antibiotics to prescribe is frequently daunting. Although these fevers would be considered nosocomial by Durack and Street and may be of infectious origin, the differential diagnosis extends well beyond the usual infectious suspects. In fact, I wonder whether these are FUOs or fevers of too many origins (FTMOs).

Decisions about which other or repeat diagnostic evaluations and procedures to undertake, whether to treat empirically for C. difficile (if that isn’t already being done), and whether to expand the antibiotic potpourri or perhaps discontinue antibiotics are not easy. The nuances and complexity of decisions regarding antibiotics are also affected by the dissonant messages bombarding physicians: the mantra that antibiotics must be used sparingly to avoid creating antibiotic-resistant bacteria versus the urgency to start antibiotics earlier while ensuring they are the “appropriate” choices (translated as “broad,” given the resistance patterns in many ICUs). When patients have been hospitalized for many months and have received numerous antibiotics but have persistent fevers, it can be unclear whether appropriate antibiotics exist or are warranted. Although some physicians sing CRP’s praises, the near-daily variation in this measure and its nonspecificity make it difficult to use to guide treatment decisions. Certainly, neither CRP levels nor procalcitonin levels help determine which cultures should be addressed with treatment. Moreover, if one chooses to use antibiotics, the question of which of the multiple bacterial isolates need to be covered is complex.

As the keeper of the antibiotics, should I be a conservative or a cowboy? Should the current antibiotics be continued, changed, or stopped? If there are no prescribed antibiotics, should I recommend some? These are interesting questions in the abstract, but there is a real patient suffering, a family with questions, and medical teams awaiting my opinion. There are no evidence-based studies and there is no guidance on which potential source of fever is the single appropriate one to treat. Frequently, the treatment approach is like playing Whac-A-Mole: positive cultures are treated sequentially — pneumonia, then catheter cultures, then urine cultures. When the fever persists, the cycle begins again.
The medical team members may be frustrated or believe they’ve exhausted the workup studies, and they may prefer not to order any more. They may not be too keen on continuing the same antibiotics. The ICU team hungers for something new and preferably simple. As I review the differential diagnosis, with disclaimers as to why any given diagnosis does or does not adequately explain the fever, I get a feeling of déjà vu. The team has heard these ruminations from me and my colleagues many times, and I suspect that by now the discussion is minimally compelling or interesting academically.

This is not the multidimensional “great case” that FUOs were once advertised to be — the cases presented on chief-of-service rounds in which an expert diagnostician pontificates about the differential diagnosis of rare or subtle disease complexes and their presentations. Given the nature of the illness in many of these patients, the conferences are more likely to be family conferences that include plans for palliative care. If the old FUOs were sometimes exhilarating, the FTMOs can be debilitating. Although some patients will recover and be discharged to lead full and active lives, many will either die or be sent to a long-term care facility.

We debate whether using antibiotics in apparently futile situations is ethical. After all, we may “create” some extremely resistant bacteria in one patient that could be transmitted to others. Alternatively, antibiotics may be lifesaving. There are few directives, ethical guidelines, or clinical pathways to follow in these cases. As I mull over the options, I am disheartened by the knowledge that whether I use or withdraw antibiotics (asking the team to observe the patient closely) or request more testing, I may simply be deferring the tough decisions for another day.

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Should Blood Be an Essential Medicine?
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According to the World Health Organization (WHO), approximately 92 million units of blood are collected worldwide each year. Given that transfusions are generally credited with saving millions of lives, it may surprise clinicians to know that blood and blood components are not included on the WHO Model List of Essential Medicines.

The Model List, established in 1977, originally included about 200 active substances. It was meant to guide countries in providing access to cost-effective medicines that are vital for public health.\(^1\) The list is revised every 2 years by a WHO expert committee. Medicines are designated as essential on the basis of their efficacy and safety, availability, ease of use in various settings, comparative cost-effectiveness, and public health need. In many countries, the list forms the basis of national drug policies. Governments and health ministries often refer to it when making decisions regarding resource allocation and health care spending. The list does not include all efficacious medicines, the latest medicines, or even all medicines needed in a country. Rather, it helps to define the minimum medicine needs for a basic health system.

Although some protein concentrates (factors VII and IX and immunoglobulins) are listed, no labile blood components are on the Model List. The reason for their absence is unclear. Certainly, the lengthy, exhaustive process for applying for a listing can be discouraging: each component requires a separate detailed, complex application. Most medicines are proposed by manufacturers with a commercial interest in having their products listed. There has been no similar advocacy for blood components that are collected and prepared by not-for-profit organizations, until now.

There are compelling reasons to add whole blood and red-cell concentrates to the list. Blood transfusion originated as a medical practice requiring either surgical intervention to join donor to recipient or a licensed practitioner to draw and immediately infuse

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