Individualized Management of Pyrexia of Unknown Origin: Will Fludeoxyglucose-positron Emission Tomography/Computed Tomography Emerge as the Imaging Common-point in the Algorithm?

Sir,

Over the years, the landscape of the "pyrexia of unknown origin" (PUO) has seen some changing trends from various aspects. These include (a) alterations in etiological spectrum, (b) changing the definition of the disease, and (c) evolution and applications of newer diagnostic modalities (both *in vivo* and *in vitro*). These changes would mandate the need to streamline the often discordant investigations (serology, cultures, and imaging) adopted in the clinical setting. Furthermore, it is important to define the place of newer techniques, namely the *in vitro* PCR techniques and novel hybrid fludeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) molecular imaging, in the diagnostic algorithm of PUO. A relatively well-defined investigational workup is the need of the hour, and a critical look at the aforementioned points would be pivotal to developing a rational algorithm.

From the etiological standpoint, there have been two notable developments: (a) among the three major etiopathologies, namely infections, malignancies, and noninfectious inflammatory diseases (NIID), there is a decreasing proportion of the former two (infection and malignancy) and increasing trend in the latter (NIID) as the cause of PUO in various studies.[1,2] Two factors at least in part could account for this change: (i) the former two causes could be better addressed by the current generation investigation modalities (both *in vitro* tests and the cross-sectional imaging respectively); (ii) furthermore, over the years, the incidence of infection has demonstrated an overall decreasing trend. The second important development was (b) subdivision of PUO into different subsets based on different characteristics, etiology and epidemiology: Subdividing the entity into four different subsets was initially undertaken by Durack and Street in 1991: (I) classical, (II) nosocomial, (III) neutropenic, and (IV) HIV related.[3] In the era of personalized medicine, this would imply that we can translate this clinically to approach these various subgroups of patients differently with individualized diagnostic algorithm that could be more focused and might yield better results and outcome.

With time, the original definition of PUO by Petersdorf and Beeson in 1961,[4] that encompassed "Fever of >38°C on several occasions for 3 weeks including 1 week in-patient investigation" has undergone modifications multiple times by various investigators as follows: (i) Durack and Street (1991) in their communication defined PUO as "Fever of >38°C on several occasions for 3 weeks including 3 days inpatient/OPD visits," while (ii) Knockaert *et al*.[5] in 2003 suggested revising it to "Fever of >38°C on several occasions for 3 weeks including a *pragmatic investigation period*," and (iii) Bleeker-Rovers *et al*.,[6,7] in 2007 defined PUO as "Protracted fever after a structured diagnostic checklist." We can conclude from these observations that there has been a reduction in the period of investigation in the time-related criterion for defining PUO, while the last study suggested a change from the time-related criterion to "a set of obligated investigations or a structured diagnostic protocol." (iv) Subsequently, Vanderschueren *et al*.[8] described a relatively less discussed entity and termed it as "Inflammation of unknown origin," defined by prolonged and perplexing inflammation with temperatures <38.3°C.

Parallel to the changes in definition and the etiological spectrum of PUO, the other remarkable change over recent years was availability and adoption of newer investigative tools particularly whole-body FDG-PET/CT imaging which demonstrated great value in evaluating patients of PUO because it accumulates in infections, malignancies, and NIIDs, the three major etiopathologies of PUO. The sensitivity of FDG-PET/CT here is a major strength and the estimated yield beyond conventional diagnostic and imaging modalities (including contrast-enhanced CT) is around 30%–40%.[1,2] In a study in an Indian setting, the overall estimated rate was found to be 38%,[9] akin to the reported literature. The major advantage can be observed in investigating NIID,[6-12] which is in recent times one of the single most identifiable causes of PUO and relatively unaddressed by the morphological cross-sectional imaging modalities. Particularly in situations such as vasculitis, metabolic FDG-PET/CT demonstrates great promise not only from diagnosis but also from the treatment monitoring viewpoint.

We have to underscore here that while the value of individualized algorithm in different clinical subsets of PUO is increasingly recognized for better patient management, the diagnostic potential of FDG-PET/CT as the imaging common point has been emphasized particularly after the basic workup (history, clinical examination, routine blood and urine samples, blood culture sensitivity, and chest X-ray) does not yield definitive diagnosis. Combined functional-structural imaging with FDG-PET/CT could address several challenging questions that would emerge in such scenario including the very important advantage of guiding biopsy.[10-12] A typical example is when rheumatological diseases present as PUO, where an uncommon presentation could be observed and early

FDG-PET/CT could be potentially useful in pinpointing the diagnosis.[12] Thus, in PUO with heterogeneous group of patients requiring an individualized algorithm, this modality has the potential to be the converging point unifying the investigational algorithm in patients with inconclusive basic workup.

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Conflicts of interest

There are no conflicts of interest.

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