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Pyrexia of Unknown Origin: Current Perspectives

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Abstract

Pyrexia of unknown origin (PUO) is a grouping of many unrelated medical conditions that share the feature of persistent unexplained fever that does not resolve spontaneously within the period for self-limited infections and whose cause cannot be ascertained despite adequate basic investigation and considerable diagnostic effort. PUO is a syndrome that has long tested the skills of physicians to achieve a diagnosis in affected patients. Patients included in this syndrome will be more difficult to diagnose as they have already resisted classification during baseline investigations. Temporal and geographical distribution of PUO cases since 1950s through 2000s revealed shift in relative proportion of specific disease categories over decades. So far, there is no standardized approach for PUO diagnosis. Evolving knowledge and the improvement in diagnostic methods, including new microbiological techniques and new instrumental procedures, necessitate a constant update of the tests included in a minimal diagnostic workup to qualify a fever as PUO.

Keywords: Pyrexia, fever, PUO.

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1. Introduction

Pyrexia of unknown origin (PUO), also known as fever of unknown origin (FUO) is a syndrome that has long tested the skills of physicians to achieve a diagnosis in affected patients. It is a grouping of many unrelated medical conditions that share the feature of persistent unexplained fever despite basic investigation. Patients included in this syndrome will be more difficult to diagnose as they have already resisted classification during baseline investigations [1]. By definition, PUO means fever that does not resolve spontaneously in the period expected for self limited infection and whose cause cannot be ascertained despite considerable diagnostic effort.

1.1 Historical overview

In 1961, Petersdorf and Beeson described the criteria for PUO that subsequently became standard. This entailed having illness of more than 3 weeks duration, fever of 38.3°C (101 F) or more on several occasions lasting at least 3 weeks and for which no cause can be identified after 1 week days of investigations in hospital or after 3 or more outpatient visits [2,3]. The temperature criteria was in order to exclude patients who may have a variable natural temperature, the 3-week duration was in order to exclude patients who had an acute infective cause that was likely to declare itself or settle spontaneously, and the inpatient investigation was included as it was felt that this would have allowed sufficient time for a reasonable performance of baseline investigations, such as imaging, culture and blood tests.

The first two criteria allow the elimination of most of the acute, self-limited diseases such as viral infection. While this classification has stood for more than 30 years, Durack and Street have proposed a revised system for classification of PUO that better accounts for nonendemic and emerging diseases, difference in clinical presentation in patients with impaired immunity, improved diagnostic technologies, and adverse reactions to new therapeutic interventions. They restratified PUO according to etiology into 4 different group: (1) classic PUO, (2) nosocomial PUO, (3) neutropenic PUO, PUO in cancer, and (4) PUO associated with HIV infection groupings that help formulate a more relevant and economical differential diagnosis, as has also been done with PUO in elderly patients and children [4]. This division is rationale as the classical PUO differs from the rest of the three entities both in the spectrum of underlying disease and the clinical approach

[5]. The second change proposed by Durak and Street was the required duration of investigation before qualifying a fever as PUO, i.e., at least 3 days in hospital or at least three outpatient visits. This reflects the greater importance given to outpatient investigation [6]. In fact, advances in the diagnostic technology and their wide spread use and their introduction in ambulatory care allowed faster access to results and the movement of medicine to a primarily outpatient model where feasible for patient comfort and cost effectiveness.

To reduce selection bias, today's definition relays on qualitative criteria of adequate and appropriate diagnostic workup (inpatient or outpatient) rather than using arbitrary quantitative time criteria with exclusion of nosocomial fever and severe immunocompromised cases.

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 PUO no longer includes the requirement for a week of inpatient evaluation. Moreover, because hospital admission is so expensive, and full diagnostic testing now can be done in outpatient settings, the definition recently was modified to remove the requirement that hospital be the setting for a week of evaluation [7].

Much of the pioneering work still persists, including the general categories of causes; infectious, neoplastic, collagen disorders (now more commonly called inflammatory) and miscellaneous; the strong recommendation of avoiding trial of therapy in most cases before adequate investigation; and the avoidance of battery ordering of tests [1].

For the purpose of management, PUO in children is only considered after a minimum of 14 days of daily documented temperature >38.3ºC after exclusion of recurrent episodes of fever with treatable cause, well documented periodic fever, and protracted but warning symptoms from acute self limiting respiratory tract infection [8].

1.2 PUO Paradoxing

It was reported in several studies that 5-15% of PUO cases defy diagnosis, despite exhaustive studies. Since the 1990s, there have been further changes in the relative distribution of these causes responsible for PUO, according to the geography and demographics of the patients described where non-infectious inflammatory diseases emerged as the most prominent diagnostic category (35% of cases in recent studies) [9]. The temporal distribution of PUO causes since 1950s through 2000s revealed a shift in relative proportion of specific disease categories during the last decade, with a remarkable increase among the inflammatory and the undiagnosed categories [1,7]. Nevertheless, it is noteworthy that recent reviews overlooked studies done in developing countries including the Middle East. So, when we did our analysis on several studies published since the year 2000 and included studies done in Egypt, the infection category appeared as the commonest causes.

Development of new diagnostic techniques, such as computed tomography (CT) scanning and improvements in microbiological recovery, has made earlier diagnosis possible and changed the relative contribution of different diseases to this syndrome [10]. Similarly, changes to demographics, such as ageing populations, and new medical treatments have changed how PUO presents and is addressed. This is seen with the now relatively low incidence of patients with PUO who have infective endocarditis due to improved blood culture systems, as well as a decrease in the use of diagnostic laparotomy now that imaging techniques, such as CT scanning, have improved detection of occult abscesses. The undiagnosed cases of PUO are increasing over time. It is paradoxical that despite the introduction of computed tomography, magnetic resonance imaging, improved culture techniques, numerous new serologic assays, and polymerase chain-reaction studies. Therefore, only difficult-to-diagnose diseases are qualified as PUO, due to the increasing availability of diagnostic facilities, both in hospital and outpatient settings. In recent years more PUOs have actually eluded diagnosis and more than 51% of cases defied diagnosis [1]. In 2003, Vanderschueren and colleagues reported that in nearly a third of 290 immunocompetent patients in Belgium, no diagnosis was made, and in 2007, Bleeker-Rovers *et al* reported that among 73 immunocompetent patients from five hospitals in the Netherlands, no cause of PUO was identified in 51% of cases [10].

The biggest change in diagnostic categories is related to a decrease in the relative proportion of collagen vascular diseases causing PUO. The reason for this change is the increase in sophisticated serological tests that render the diagnosis of collagen vascular diseases more accurate and diagnosed earlier, thus those accompanied by fevers of prolonged duration do not remain undiagnosed, and therefore do not fulfill the criteria of an PUO[11].

In resource poor countries PUO is more frequently due to infections comparing to high resource countries where inflammatory and malignant disorders account for most of the cases. This may partly represent differences in the geographic and temporal distribution of diseases, but is also explained by the comprehensiveness of the investigations performed prior to classifying a patient as having PUO and the diagnostic tests subsequently available to investigate it. For example, the availability of highly sensitive blood culture techniques and high quality echocardiography means that bacterial endocarditis is now a less common cause of PUO because the condition can be

diagnosed relatively easily and is therefore unlikely to meet the PUO criteria.

It is noteworthy that all publications of 1990s used the old definition (1 week of in-hospital investigation) which resulted in selection bias in favour of unsolvable cases. When, for instance, a thoracoabdominal helical computed tomography, performed on the first or second hospitalization day or at first or second outpatient visit, showed a tumour, abscess or others, fever no longer qualified as PUO[12].

Moreover, many modern cases are in complex patients with multiple possibilities, with one authority coining the term 'Fever of Too Many Origins' [7].

Table 1: Summary of recent studies on PUO patients performed in 2000-2017

Study	Country	Year of study	Population	Total cases	Etiological cause %				
					Infectious Diseases	Inflammatory	Malignancies	Miscellaneous	Undiagnosed
Mansueto[13]	Italy	1991–2002	Adult	91	32.0	12.0	14.0	10.0	32.0
Zenone[14]	France	1999–2005	Adult	144	23.0	26.0	10.0	15.0	26.0
Hot[15]	France	1999–2005	Adult	280	11.0	27.0	20.0	9.0	33.0
Efstathiou[9]	Greece	2001–2007	Adult	111	30.0	33.0	11.0	5.0	21.0
Bleeker-Rovers[10]	Netherland	2003–2005	Adult	73	16.0	22.0	7.0	4.0	51.0
Vanderschueren[16]	Belgium	2000–2010	Adult	436	17.0	24.0	11.0	10.0	39.0
Sandoval[17]	Spain	2007–2012	Children	153	60.1	3.3	3.3	1.3	32.0
Pedersen[18]	Denmark	2005–2010	Adult	52	19.0	33.0	8.0	0.0	40.0
Iwanczak[19]	Poland	2007	Children	10	50.0	20.0	0.0	30.0	0.0
Bakashvili[20]	Georgia	2003–2005	Children	52	77.0	3.8	3.8	1.9	13.5
Kim[21]	South Korea	2000–2014	Children	100	19.0	15.0	8.0	15.0	43.0
Kasai[22]	Japan	2002–2006	Children	960	19.8	46.6	7.0	12.8	13.8
Naito[23]	Japan	2011	Adult	121	23.1	30.6	10.7	12. 4	23.1
Chin[24]	Taiwan	2001–2002	Adult	94	57.0	7.0	9.0	9.0	18.0
Cho[25]	Taiwan	2002–2012	Children	126	27.0	12.7	16.7	19.8	23.8
Chien[26]	Taiwan	2006–2014	Children	93	37.0	14.0	17.2	16.1	15.1
Zhiyoung[27]	China	2001	Adult	208	31.7	22.1	16.8	5.3	24.0
Hu[28]	China	2002–2003	Adult	142	36.0	32.0	13.0	5.0	14.0
Joshi[29]	India	2006–2007	Children	49	69.4	2.0	12.3	4.0	12.3
Bandyopadhyay[30]	India	2008–2009	Adult	164	55.8	7.4	22.0	3.6	12.2
Shantaram[31]	India	2013	Adult	100	60.0	24.0	10.0	6.0	0.0
Mir[32]	India	2010-2012	Adult	91	43.9	12.1	12.1	4.5	27.4
Ikhlas[33]	India	2012–2013	Children	53	69.8	3.8	15.1	0.0	11.3
Saltoglu[34]	Turkey	1994–2002	Adult	87	59.0	18.0	14.0	2.0	7.0
Kucukardali[35]	Turkey	2003–2004	Adult	154	34.0	34.0	14.0	5.0	16.0
Coplan[36]	Turkey	2001–2004	Adult	71	45.0	27.0	14.0	6.0	9.0
Cogulu[37]	Turkey	1996-2001	Children	80	59.0	2.0	5.0	20.0	13.0
Ciftci[38]	Turkey	1995-2002	Children	102	44.2	11.7	6.8	24.5	12.8
Tezer[39]	Turkey	2005–2007	Children	77	45.4	13.0	6.5	24.7	10.4
Mete[40]	Turkey	2001–2009	Adult	100	26.0	38.0	14.0	2.0	20.0
Mahmoudi[41]	Iran	2004–2006	Children	95	26.3	6.3	7.4	8.4	51.6
Solimani[42]	Iran	2006–2012	Children	1100	55.1	4.6	6.7	23.3	10.3
Abdelbaky[43]	Egypt	2006-2008	Adults	100	50.0	24.0	8.0	7.0	11.0
Hassan[44]	Egypt	2006–2011	Children	127	36.2	10.2	7.9	29.9	15.8
Ali-Eldin[45]	Egypt	2009–2010	Adult	93	42.0	15.0	30.0	0.0	12.0
Montasser[46]	Egypt	2015	Adult	374	66.3	7.2	7.2	11.5	7.8
Kabapy[47]	Egypt	2009–2010	Adult	979	64.4	30.0	0.9	2.2	3.2
Total				7242	41.6	18.2	10.8	9.9	19.6

Years in red font indicate the year of publication

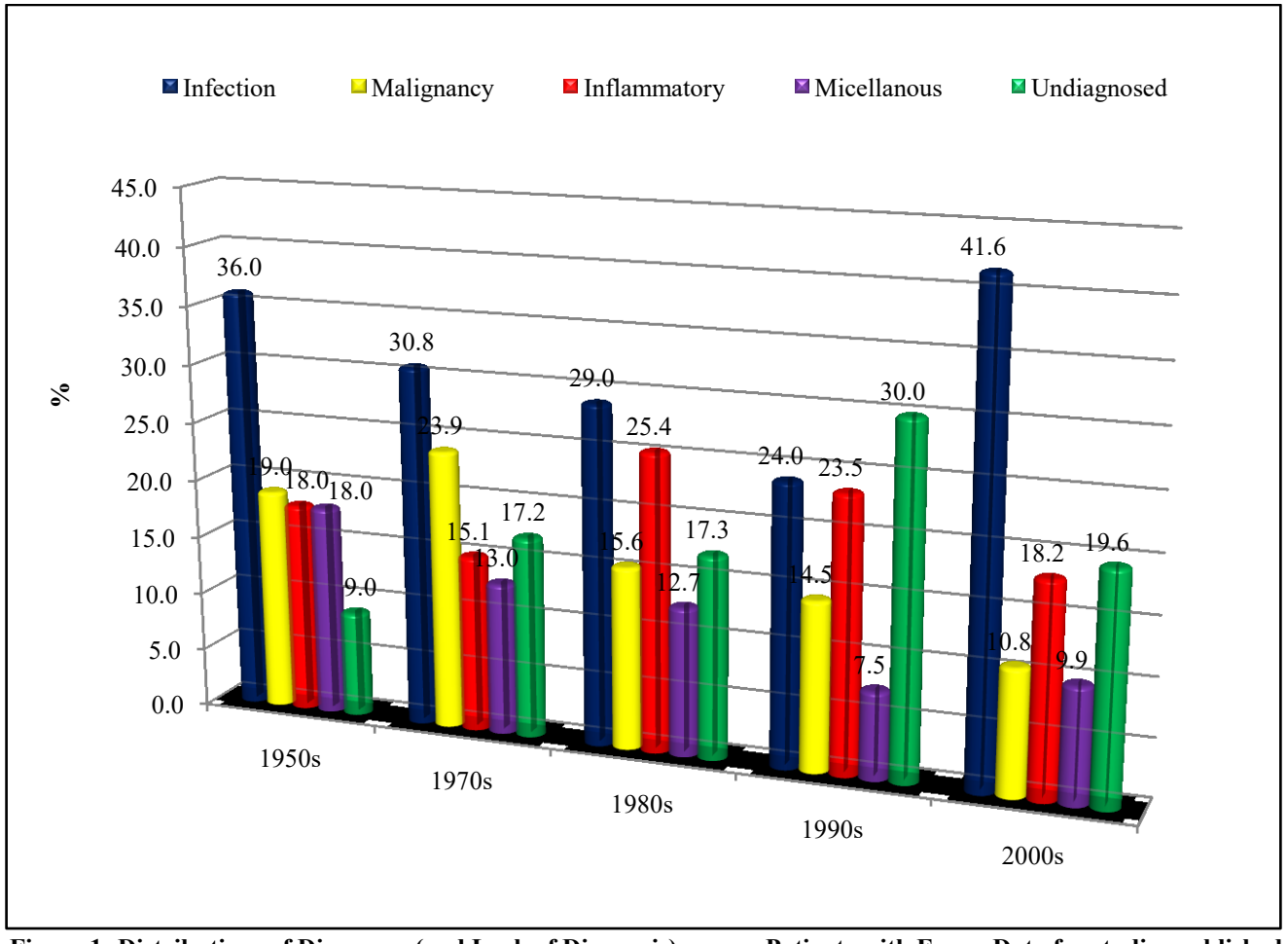

Figure 1: Distributions of Diagnoses (and Lack of Diagnosis) among Patients with Fever. Data for studies published in 1950s through 2000s

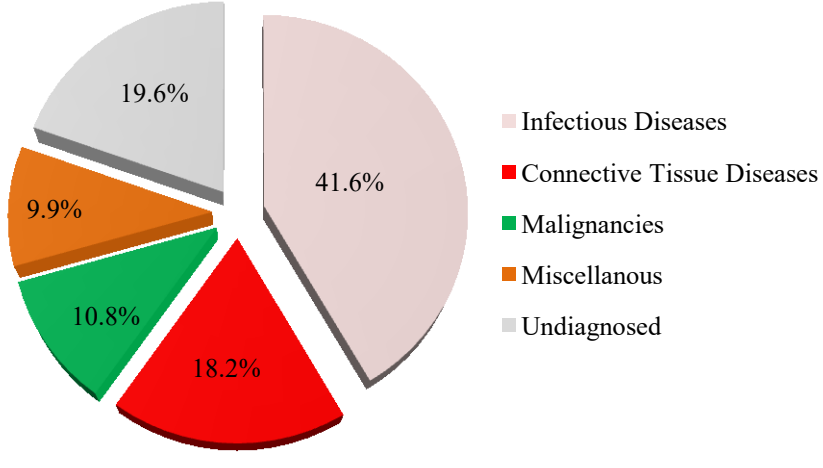

Figure 2: Distribution of PUO according to etiological category

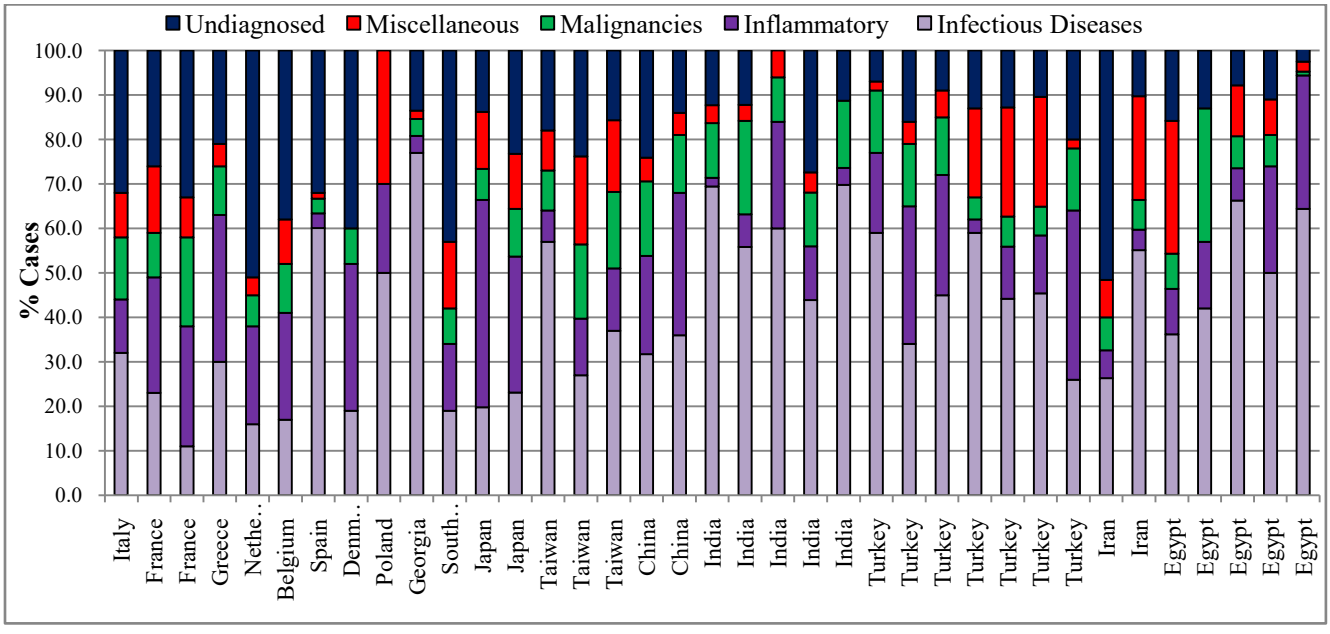

Figure 3: Distributions of Diagnoses (and Lack of Diagnosis) among Patients with PUO. Data for studies conducted between 2000 and 2017

2. Fever of Unknown Origin to Fever of Too Many Origins

Horowitz, an infectious-disease physician at a tertiary care facility in the metropolitan New York described new PUOs that 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 and radiological findings are diverse and cannot rule out infection. Therefore, determining the cause of a fever and which antibiotics to prescribe are 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 making it difficult to state whether these are PUOs or fevers of too many origins (FTMOs). Decisions about which other or repeat diagnostic evaluations and procedures to undertake, whether to treat empirically, and whether to expand the antibiotic or perhaps discontinue antibiotics are not easy. Thus, if the old PUOs 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 [7]

3. Prevalence and Etiology of PUO

The prevalence of PUO among adult hospitalized patients is reported to be 2.9% [48]. With the recent advances in diagnostic aids, true PUO is becoming uncommon in some developed countries. In Netherlands, where only 73 cases of PUO were registered between December 2003 and July 2005 at 950 bed academic referral hospital and 2800 bed community hospitals [10]. In France a total of 144 PUO cases were reported between 1999-2005 [14]. However, in Egypt, a total of 979 PUO cases were admitted in a fever hospital in one year. Over 200 causes of PUO have been described in the literature [49]. The original categories for the diseases that cause classic PUO are robust and are still in use today. According to studies conducted to date, the diseases taking part in PUO etiology and their rates are as follows: infections (21–54%), noninfectious inflammatory causes (13–24%), neoplasms (6–31%) and other causes (4–6.5%). The incidence of various causes differ with geographical, age and sex difference and development level of countries, vector distribution the availability of diagnostic tests and the experience of clinicians [1, 7, 50, 51]. Misleading factors in the diagnostic approaches made by the physician; regarding the anamnesis (24.6%), the clinical examination (22.6%), the wrong interpretation of a laboratory test (20.7%), and inadequacy in the evaluation of a symptom and/or a positive test (5.6%).

A list of the more common diseases from each category is given in Table 2.

Infection still remains the most common cause of classical PUO all over the world even though the demographics vary from region to region. The rate of disease attributable to each category varies between different populations studied and the type of healthcare environment, but in general, in developed countries, infectious causes account for 17–35%, noninfectious inflammatory diseases account for 24–36%, neoplastic causes for 10–20%, miscellaneous causes 3–15%, and no diagnosis established in 16–39% [4,7,49,52-55]. In developing countries, infections are the major cause of PUO, whereas in developed countries NIID account for most cases. In several recent studies no cause could be found in a large proportion of patients [10,16,18,52,56]. Lower incidences of specific infections, such as tuberculosis and brucellosis, and differences in availability of modern imaging techniques, such as CT, MRI and FDG-PET/CT, may among others cause these differences.

Table 2: Classic causes of fevers of unknown origin [1,7,49,50,53,54,57]

Infections	Neoplastic	Inflammatory	Miscellaneous
Bacterial Tuberculosis (extra pulmonary, miliary, bovine), Nontuberculous mycobacteria *Brucellosis, Salmonellosis, Bartonellosis, Tularemia*, *Listeriosis*, Q fever, Ehrlichiosis Chronic otitis media, Sinusitis, Mastoiditis Dental abscess Culture-negative endocarditis Occult abscess (abd/pelvic) Complicated UTI, Pyelonephritis, Obstructive uropathy Osteomyelitis Mycoplasma Pneumonia Whipple's disease Actinomycosis Rat-bite fever, DF2 Yersiniosis **Spirochetal** Syphilis (Venereal/endemic), Yaws, Pinta, Leptospirosis, Lyme disease, louse borne relapsing fever **Rickettsial** epidemic/murine endemic typhus, Scrub Typhus, Rocky Mountain spotted fever **Chlamydial** Psittacosis **Viral** HIV, EBV, CMV, Dengue, HBV, HCV **Fungal** Aspergillosis, Coccidioidomycosis, Blastomycosis, Cryptococcosis **Parasitic** Malaria, Visceral leishmaniasis, Babesiosis, Toxoplasmosis Visceral larva migrans Amebiasis, Trichinosis	Lymphoma (HL/NHL) Leukemia (ALL/AML/CML/CLL) hepatoma, Hepatocellular carcinoma or liver metastases Hypernephromas Langerhans cell histiocytosis Ewing sarcoma Renal Cell carcinoma Wilms' tumor Neuroblastoma Reticulum cell sarcoma Myelodysplastic syndrome Atrial myxoma	Adult-onset Still's Disease (AOSD)\RA, SLE, Sarcoidosis Temporal arteritis (Giant Cell arteritis) Behcet's disease Granulomatous colitis Granulomatous hepatitis Acute rheumatic fever Periarteritis nodosa/Polyarteritis nodosa Erythema nodosum Henoch–Schönlein purpura Hyperimmunoglobulin D syndrome Kikuchi–Fujimoto disease Muckle–Wells syndrome FAPA syndrome (Periodic fever, cervical adenopathy, pharyngitis, and aphthous ulcers) Familial Mediterranean fever Rosai–Dorfman disease Serum sickness Wegener's granulomatosis Takayasu's arteritis Pseudogout Polymyalgia rheumatic (PMR) Kawasaki disease Inflammatory bowel disease (Crohn's disease)	Factitious fever (Munchausen) Drug fever (antibiotics, anti-epileptics, NSAIDs, anti-arrhythmics) Alcoholic hepatitis Hyper-IgD syndrome Habitual hypothermia Disordered heat homeostasis ("central fever") Endocrine disease (hyperthyroidism, adrenal insufficiency, pheochromocytoma) Icthyosis Chronic hemolytic anemia Chronic salicylism Schnitzler's syndrome Aspiration pneumonitis Weber–Christian disease Fabry's disease Pseudolymphomas Familial dysautonomia Hirschsprung's disease with enterocolitis Neimann–Pick disease Pulmonary embolus Sickle cell and hemoglobinopathy crisis Blue diaper syndrome Cyclic neutropenia Cirrhosis pulmonary embolism DVT

In India 2014[32], A total of 91 cases (62 males and 29 females), with age ranging from 16 to 80 years were investigated. The mean duration of fever before hospitalization was 26±4 days. The etiology of PUO was delineated in (66%) of cases, whereas, (25%) remained undiagnosed. Most common group of PUO was that of infectious diseases (44%) followed by collagen vascular diseases and malignancies (12 % each). Amongst the infection group, brucellosis and salmonellosis comprised the majority of cases (25% each).

Infections remain the predominant cause of PUO in Egypt; however, the causative agents have changed over the last 40 years. The proportion of undiagnosed cases of PUO seems to be lower than what it was in the past due to advances in diagnostic technologies. Finally, clinicians must be aware that the etiology of PUO varies across demographics, geography, and time. Accordingly, reporting local cases is important in informing clinicians about the epidemiologic pattern [45-47].

In Egypt, recent prospective hospital based studies had analyzed the clinical spectrum of PUO among adult Egyptian patients. Among patients admitted to Ain Shams University Hospitals during the period from May 2009 till the end of December 2010. All Egyptian patients fulfilling the criteria of PUO admitted during this period were followed up till reaching the diagnosis. 93 patients were

included in the study. They were 48 (51.6%) females and 45 (48.4%) males, their ages ranged from 15 to 65 years (34.39±13.6). Infections were the commonest cause of PUO (41.94%) followed by malignancies (30.11%). While autoimmune diseases represented 15.05% and in 12.9% of patients the diagnosis was not established. Brucellosis and infective endocarditis were the commonest infections, while hematological malignancies were the commonest oncological diseases. Systemic lupus erythematosus (SLE) was the commonest auto-immune disease. Brucellosis, infective endocarditis, hematological malignancies and SLE must be considered in the differential diagnosis of adult PUO in Egypt [45].

The spectrum was quite different in a similar study conducted at Alexandria Fever hospital during the same study year where infectious causes for PUO represented more than two thirds of the cases after adopting the old definition of PUO. This was exactly similar to the percentages reported by Montasser *et al*, in a retrospective study conducted in Abbassia Fever Hospital, nevertheless they adopted the new definition of PUO [46]. The percentage of infection was higher among drug abusers included in the study where 78% of them were diagnosed with infectious disease comparing to non-abusers (62%). Malignant causes were diagnosed in 2% and other miscellaneous represented 8% and 8% were left undiagnosed comparing to 0.8%, 1.6% and 2.8% respectively in non-abusers. A similar percentage to that reported in Ain Sham study (30.3%) were diagnosed with an autoimmune disease, the number of patients diagnosed with malignancies were much more lower to that reported in Ain Shams study (0.9%). About 2.2% of cases were diagnosed with miscellaneous conditions.

In another study aimed to estimate the prevalence of connective tissue diseases among patients presented with PUO to the internal medicine department, Ain Shams University hospital, Out of 100 PUO patients, 50% were found to have infectious diseases, 24% were found to have connective tissue diseases, 8% miscellaneous causes and 7% neoplastic diseases. In 11 patients no definite cause for PUO could be identified. Connective tissue patients were: systemic lupus (33.3%), familial mediterranean fever (20.8%), rheumatoid arthritis (16.6%), Still's disease (12.5%), Rheumatic fever and Behcet syndrome/Crohn's disease (4.3%) [43].

The increased prevalence of connective tissue diseases in patients presenting with PUO in Egypt should be kept in mind and should raise the attention for early detection of the symptoms and signs of these diseases. Environmental pollutions, lifestyle modifications and other unidentified triggers may play a role in this increased prevalence [43, 45-47].

Comparing the result of studies conducted in Egypt with those conducted in other countries worldwide reveal that there is a higher occurrence of infectious diseases in study population. On the other hand, the percentage of cases which were not diagnosed was extremely lower than the global rates, even in the developed countries. Most probably, many cases were misdiagnosed as an infectious disease without reaching a definitive diagnosis. Patients usually improve with symptomatic treatment, and get discharged as cured cases and reported in records as the most probable diagnosis might be. Probable causes for the variability are the geographical location, habits of local population and availability of diagnostic tools and finance to reach a convincing final diagnosis. In study conducted by Kabapy *et al*[47] in Alexandria, a very high percentage of patients (over 50%) were diagnosed with respiratory tract infections. This may be attributed to a problem with antimicrobial group used with these patients, as most of these patients were cured just by switching to a more appropriate antimicrobial group. Compliance of the patients to the antimicrobial treatment raises other questions about the warranty of antimicrobial drug usage as over-the-counter medications in Egypt. A further study of antimicrobial usage and resistance is warranted to investigate the current situation in Egypt. Moreover, in many studies, more sophisticated laboratory techniques for detecting auto-antibodies were used to reach a finer diagnosis of non-infectious inflammatory diseases. In the studies conducted in Egypt, mainly ANA and RF were used to reach the diagnosis of autoimmune disease. In many other studies, ANCA, Anti Ds-DNA, Anti-Ro and Anti-La were used to reach a finer diagnosis. Uses of more sophisticated laboratory techniques are warranted to reach a more accurate final diagnosis.

Interestingly, the percentage of cases which were not diagnosed (3.2%) in the study conducted in Alexandria was extremely lower than the that reported in other studies conducted either in Egypt or worldwide which varied between (7.0%-52.0%; most frequently 15-25%) even in the developed countries. (Table 1), Most probably, many cases were misdiagnosed as an infectious disease (as supported by response to the empirical antibiotic therapy that was given to 90% of the cases) without reaching a definitive diagnosis. Patients usually improve with symptomatic treatment, and get discharged as cured cases. This may also be attributed to that patients were referred after extensive investigations elsewhere, and thus we can speculate that more difficult-to-diagnose cases are referred. Another explanation is that physicians may be rushed to reach a probable final diagnosis even if it is inaccurate and not unsupported by laboratory investigations or the imaging techniques. This may be also attributed to shorter duration of stay in the hospital when compared to other studies and that almost 13% of patients were discharged at their request probably due to insufficient services and facilities in the hospital [47].

The diagnosis of PUO is more frequently reached before 3 weeks have elapsed because patients with fever tend to seek medical advice earlier and because better diagnostic techniques, such as CT or magnetic resonance imaging, are widely available resulting in more hard-to-diagnose cases meeting the definition of PUO. Another contributing factor, as suggested by Vanderschueren *et al*., could be the observation that most patients with PUO without a diagnosis do well, which may lead to a less aggressive diagnostic approach in clinically stable patients once diseases with immediate therapeutic or prognostic consequences have been ruled out to a reasonable extent. This could be especially true for patients with periodic fever who are asymptomatic in between febrile episodes[16].

Importantly, the longer the duration of the fever, the less likely it is that the aetiology is infectious in nature. In one study of adults, there were no significant relationship between fever duration and the etiology of PUO [58]. In another study of adults, Yu *et al*.,[59] reported that the infection group had a relatively shorter average duration of fever than the other groups.

Demographic and geographic considerations need to be factored into the diagnostic approach to avoid needless or misdirected diagnostic testing. With PUO patients, there are almost always one or, more clues from the history and physical examination or nonspecific laboratory tests that suggest a disease category in general, or more specifically, a number of diagnostic possibilities [30]. Geographic location has a major influence on the distribution of the causes of PUO. For example, Visceral leishmaniasis in endemic areas is a major diagnostic consideration with PUO, whereas in nonendemic areas, visceral leishmaniasis should not be considered in the differential diagnosis of PUO in HIV patients [53]. In the Mediterranean area, adults' infections (40% of cases) and cancer (25% of cases) account for most of Fevers of unknown origin. Autoimmune disorders account for 10-20% of cases, others (drugs, factitious, etc.) account for 10% of cases and 10% of cases remain undiagnosed [13]. While in children; 30-70% of cases are due to infections, 5-10% cancer and autoimmune disorders account for 10-20%. In Saudi Arabia, Infectious diseases, especially TB, continue to be the leading etiology of PUO[60].

Some authors identified smoking and added previous use of antibiotics as a risk factor for infectious diseases [14,35,50]. In the study conducted by Kabapy *et al*, in Egypt, statistical analysis and risk estimation showed that it is more likely for cases of PUO to be diagnosed with an infectious disease if the patient was a smoker, had contact with animals or birds, a drug addict or HIV positive. And, it is more likely for cases of PUO to be diagnosed with an autoimmune disease if the patient was a female. Risk factors are important to help steering the diagnosis towards one of the final diagnosis of PUO. This high use cases of penicillin in 90% of PUO cases in this study, show that clinicians had provisionally diagnosed most of the PUO as infections. This in many cases is not true and raises issues like drug resistant bacteria, drug tolerance by patients [47].

4. PUO in select populations

4.1 PUO in children

PUO in pediatrics have a different distribution of disorders than reviews of elderly patients with PUO. This changes in the relative distribution of causes responsible for PUO are primarily due to the improvement in diagnostic testing rather than to a major shift in the relative incidence of the general categories [57]. To enable adequate comparison between PUO studies, using a uniform definition and uniform entry criteria is very important. Selection bias increases when patients presenting to the outpatient department are included, because prospective case finding is harder and standardized diagnostic protocols are more difficult to implement. Furthermore, many differences in management and diagnostic facilities exist among hospitals or countries.

Febrile illnesses are much more common in children than adults, but most episodes of fever are short-term and resolve spontaneously, and/or are associated with a detectable source of infection. Considerations of PUO in childhood are loosely based on Petersdorf and Beeson's 1961 definition in adults of >3 weeks of illness with fever > 38.3ºC on several occasions persisting without diagnosis, despite medical evaluation. Series of pediatric patients with unexplained fever have used shorter duration (8 days) of fever without explanation after initial evaluation [61].

It is now generally accepted that unexplained fever that persists longer than 1 week in a child warrants preliminary investigations as fever from viral infections generally resolves within that time frame [8]. The number of infectious and noninfectious etiologies of PUO in children is extensive. PUO is usually caused by common disorders, often with an unusual presentation [62]. The current incidence of pediatric PUO varies among studies. Cho *et al*[25] reported the incidence of pediatric PUO is between 0.5% to 3% and Antoon *et al*[63] reported its incidence remain unclear. However, the incidence was reported by Chow *et al*., in his systematic review to range from 12% to 24% [8]. In a retrospective study conducted between 2006 and 2011 at Mansoura University Children Hospital in Egypt, the incidence was 15.7%. Although this was a hospital based study, this hospital receive and provide care for patients referred from 5 nearby governments with a population of about 15 million [44].

It was well known that the three most common etiologic categories of PUO in children in order of frequency are infectious diseases, connective tissue

diseases, and neoplasms. In addition, there are causes of PUO, such as drug fever, factitious fever, central nervous system dysfunction, and others, that do not fit into the above categories. However, the causes of PUO have changed over the years and have been influenced by diagnostic techniques. Due to the development of improved diagnostic techniques, the proportion of PUO caused by infectious diseases has tended to decrease and the proportion of CTD, malignancies, and other diseases has tended to increase. In many cases, a definitive diagnosis is never established and fever resolves [21,37,64]. Although it has been known that infectious disease was most common cause of pediatric PUO in the past, undiagnosed portion of PUO have now increased due to development of diagnostic techniques for infectious diseases. In a study done at Samsung Medical Center in South Korea, a total 100 patients with PUO were identified. Confirmed diagnosis was achieved in 57 patients (57%). Among them, infectious diseases (19%) were most common, followed by connective tissue diseases (15%), necrotizing lymphadenitis (8%), and malignancies (7%). Children with fever duration over 28 days had a trend for higher frequency of connective tissue diseases (28.3%) except undiagnosed etiology. The symptoms such as arthritis, lymph node enlargement and only fever without other symptoms were significantly related with connective tissue diseases, necrotizing lymphadenitis and undiagnosed respectively. The undiagnosed patients made up the greatest proportion of PUO cases [21].

In Egypt, in a hospital based study conducted retrospectively, 127 patients met the diagnostic criteria. Infectious diseases were the commonest causes of PUO in 46 cases (36.22%) followed by the miscellaneous causes in 38 cases (29.9%). Meanwhile, collagen vascular diseases and malignancy were diagnosed in 10.2% and 7.87% respectively. FMF is the most common among the miscellaneous causes and it is a relatively common diagnosis in our locality. The disease was considered after exclusion of all other causes of PUO and if the family history, clinical and laboratory findings were suggestive. Cases were confirmed by genetic study for MEFV mutation. Other miscellaneous causes included PFAPA syndrome, Churge Strauss syndrome, and autoimmune hepatitis. In all cases, the diagnosis was established by non-invasive means in more than two-third of the case. While rest of patients required invasive procedures like biopsy, bone marrow aspiration, About 15.75% remained undiagnosed [44].

Chow and Robinson [8] summarized 18 studies on pediatric PUO in a systematic review in 2011. Eight studies were performed in developed countries (USA, Spain, and Germany) and published from 1970 to 1998. The other 10 studies were performed in developing countries and published from 1994 to 2008. In summary, infectious disease (51%) was the most common cause, although 22% of cases were undiagnosed. Among the ten studies in developing countries, infectious disease was the most common etiology (36% to 78%). Among the eight studies in developed countries, infectious disease was the most common etiology in 6 studies and no diagnosis was most common etiology in 2 studies that were performed in the United States. Similarly, in a previous Korean study from 1999 to 2004, infectious disease was also the most common etiology (41.7%), and 27.5% of patients were undiagnosed.

Recent studies have revealed that the proportion of undiagnosed cases has increased over time due to improved diagnostic technique. It is thought that improved techniques make it easier to diagnose certain diseases earlier before the patient meets criteria for PUO [8].

Since the development of diagnostics has been rapidly evolving in many areas of medicine, including infectious diseases, it may not be accurate to combine data from earlier years with data after 2000, when more advanced diagnostic methods became available in clinical practice. Bacterial infections (59% of all infections) were the most common, and viral infection made up only 7-8% of all infections. Among viral infections, Epstein-Barr virus was the most common viral pathogen [8, 33].

Chow and Robinson concluded that there was difference in the types of infections responsible for pediatric PUO between developing and developed countries. Bartonella infection was more common in developed countries, while brucellosis, typhoid fever, and tuberculosis were more common in developing countries. Many studies emphasized that tuberculosis should be considered to be a cause of PUO in endemic countries [65, 66].

CTD is the second most common cause of PUO in many studies. Among these, JIA was most common, followed by SLE. while various CTD such as autoimmune cholangitis, polyarthritis nodosa, and rheumatic fever have been reported in another study [67].

Joint disease in children with PUO suggests a serious underlying disorder such as connective tissue disease (CTD), endocarditis or leukaemia. Still's disease, an important cause of PUO in children, can also affect young adults and is a condition often neglected during the search for a cause.

Malignancy is a relatively uncommon cause in children and young adults, but lymphoma is a potential diagnosis which is important to exclude because delay in diagnosis may adversely affect prognosis [68].

Regarding the duration of fever, except undiagnosed etiology, the percentage of CTD was highest in patients who had fever>28 days and the percentage of infectious disease was highest in patients who had fever≤28 days [21]. In another pediatric study, there was no

difference in the frequencies of CTD in patients with fever 14–30 days and in patients with fever over 30 days [25].

Children with cyclical or recurrent fevers should also be defined separately from PUO in that different diagnostic considerations apply, and hence, different approaches to the evaluation are employed. Irregular episodes of febrile illnesses raise issues of recurrent infections and possible immune deficiency syndromes, inflammatory bowel disease, or systemic onset juvenile rheumatoid arthritis. Episodes of fever that occur in predictable cyclical intervals, with each episode typically 8 days' duration, might lead to consideration of FAPA (fever, abdominal pain, pharyngitis, adenitis and/or aphthous ulcers) syndrome[69], familial Mediterranean fever, cyclical neutropenia, and hyper-IgD syndrome. Although there are no definite diagnostic criteria for FAPA syndrome, episodes usually occur in three- to four-week cycles that are so regular parents can predict the timing of the next fever. Children with this diagnosis are entirely well between episodes, and no one around them gets ill before or after them, as a rule. This may be the most common recurrent-fever syndrome in otherwise healthy children [70].

5. Difference between adult and pediatric PUO

A major difference between adult and pediatric PUO is prognosis. The prognosis of pediatric PUO is good compared to PUO in the adult due to differences in etiologies. Even if pediatric PUO remains undiagnosed, many cases resolve spontaneously [21]. In the study conducted by Kim *et al*., 92 patients (92%) were no longer febrile by the time of discharge, but almost all patients who had persistent fever eventually improved after discharge. Only 1 patient (1%), who was diagnosed with HLH (hemophagocytic lymphohistiocytosis), died despite receiving appropriate chemotherapy. In another study, Cho *et al* [25] reported that 9 of 126 patients (7.14%) died, and none of the patients who remained undiagnosed had unfavorable outcomes. Four of 91 patients (4.4%) died in Park *et al*., study [71]; 1 patient had HLH, 1 had acute respiratory distress after adenoviral infection, and 2 had been not diagnosed. The original studies on pediatric PUO from the 1970s reported a mortality rate of 6% to 9%4), but the etiologies and mortality rates may have changed since then. Therefore, further study is needed to understand the trends in mortality and overall outcomes associated with pediatric PUO. A cause is not found in over 40% of children under 18 years with PUO compared with less than 5% for adults over 65 years. Many children with PUO recover without a diagnosis ever being established [8,17, 66, 68,71].

5.1 PUO in elderly

Infections in older persons may present in atypical, nonclassical fashions. This is important because of the high impact of infectious diseases on this vulnerable population. Older persons are more susceptible to infections and, in turn, infectious diseases are associated with higher morbidity and mortality rates compared to a younger population. Multiple factors are thought to be responsible for the higher incidence and elevated morbidity and mortality rates for infections in older persons. These include diminished physiologic reserves, as well as the immunity. Decremental biologic changes with age, including changes in renal and hepatic function, which alter the pharmacokinetics and pharmacodynamics of drugs and comorbidities that diminish host defenses and mask the clinical presentation of infections. The geriatric patient is likely to suffer from more than one chronic disease and is usually taking multiple medications that may affect host defenses and increase the risk of adverse drug reactions, including-drug induced fever. An atypical presentation of an infection in the older patient may delay diagnosis and delay the initiation of empiric antimicrobial therapy in a patient who is already compromised by aging and chronic diseases. The most important clinical diagnostic clue to the presence of infection is fever, and this cardinal sign of infection may be blunted or absent in up to a third of infected older persons. Conversely, the presence of a fever and/or the presence of a leukocytosis in a geriatric patient are more likely to be associated with a serious bacterial or viral infection than it is in a younger febrile patient [72].

Haematologic malignancies and solid tumours are more common causes of PUO in elderly patients than in younger adults. Infections and CTDs are also frequent causes in the elderly. Temporal arteritis and polymyalgia rheumatica are particularly common in this age group. Symptoms of temporal arteritis may be non-specific, such as lethargy and general malaise, which may result in diagnostic delay and risk of blindness from retinal artery occlusion. Endocarditis as an infectious cause for PUO occurs more often in elderly. This might be contributed to the fact that the older patients more often had sepsis (28%). In fact, the changes in cardiac valves and diminished vascularisation are more common in the elderly, which are also suitable for the onset of infection. Hence one should consider it while planning diagnostic procedures and echocardiography should be included into the regular diagnostics of PUO in the elderly. Many causes lead to the penetration of bacteria into blood and to a thread of pathogenic events, and finally sepsis. Some of them are physiological weakening of barriers in the elderly, as well as multiorganic dysfunction, especially of vital organs [73]. Tuberculosis accounted for 60% of all the infectious causes and empirical anti-tuberculous treatment served as a diagnostic method in 43% of the cases with tuberculosis [74].

The diagnostics of PUO in the elderly often differs from the one in young patients. The manifestation of a

disease is often nonspecific in older patients. Many other comorbidities exists that determine the further diagnostics and treatment, and hence the outcome of the illness. The symptoms and signs of many illnesses are atypical, or less prominent in older patients, which obviously complicate diagnostics. Thus for instance, cognitive function disorders can be the only sign of infection in the elderly. The undetermined cause of PUO can reach 30%. One possible explanation might be that the decrease of temperature occurred faster in the young, more often leading to complete recovery without the final diagnoses. The other reason might be that the elderly exhibited prominent signs of some diseases sooner, while it sometimes took months to confirm a diagnosis clinically or by laboratory tests [12,68, 73,75]. Turkulov and co-workers found that the outcome was more favourable for the control group (92%), than for the elderly (56%). While no fatal outcome occurred in the young, while it did in 12% of the elderly, with sepsis as the most common cause as the older patients have diminished clinical response to infections, as well as malignant and systemic diseases. Multimorbidity occurs very frequent in this age. Moreover, the immune system, cellular as well as humoral, is weakened in the elderly. These considerably contributes to the unfavourable outcome of many illnesses [73].

5.2 PUO in pregnancy

Any acute or chronic infectious diseases may be contracted during the course of pregnancy, and conception may occur in women already subject to infection. The coexistence of pregnancy may aggravate the risk to maternal life of the more serious of these diseases. In pregnancy most infections are no more common, nor more serious than in non-pregnant women of similar age. Besides affecting the mother, some infections may be transmitted to the fetus in utero, during the intrapartum period or, postnatal, with potentially serious consequences. Infectious illnesses and fevers in the mother must be treated as any other serious illness. The effects on pregnancy depend on the extent of temperature elevation, its duration, and the stage of fetal development when it occurs. Mild exposures during the preimplantation period and more severe exposures during embryonic and fetal development often result in miscarriage, premature labor, growth restriction, and stillbirth [76, 77].

Postpartum fever is a common problem for obstetricians, PUO occurring in the puerperium may be relatively unfamiliar and a challenge to the majority of obstetricians. Although a uterine leiomyoma as a cause of fever in the puerperium is not new, rarely does it cause prolonged fever. It should be taken into consideration in pregnant women known to have uterine myomas during pregnancy and in the puerperium, especially if PUO develops. Nonsteroidal antiinflammatory drugs can be a tool for making the differential diagnosis in such a patient, and exploratory laparotomy can be delayed until an emergency condition occurred, especially important during pregnancy [78]. Milne *et al* reported a case of *Plasmodium vivax* malaria, despite not having travelled to an endemic malaria area for over 1 year. She had deranged liver function tests, evidence of hemolysis and low platelets on admission. Differential diagnosis included haemolysis, elevated liver enzymes and low platelets syndrome; cholestasis of pregnancy or a viral infection [79]. *P vivax* has a significant impact on outcomes of pregnancy. In 2570 women, there was a 16.8% parasitaemia at the time of delivery with either *P falciparum* or *P vivax* mono-infection. *P falciparum* malaria was associated with a significant decrease in birth weight and hemoglobin level (Hb<7 g/dl). *P vivax* was also associated with a lower birth weight and severe anaemia [80]. Therefore, although the outcomes for *P falciparum* are more severe those for *P vivax* are significant. Non-falciparum malaria in pregnancy can be controlled by weekly chloroquine. Primaquine in pregnancy should be avoided because it is not known if baby has glucose-6-phosphate dehydrogenase (G6PD) deficiency and therefore risk of haemolysis [80].

5.3 Pseudo-PUO

Pseudo-PUO typically occurs when a child develops a series of benign, self-limited illnesses over a short period of time. Often this begins with a well-remembered acute illness with higher fever than is usual (and, occasionally, a febrile seizure). The fever abates over an expected period of time, but vague persistent symptoms, perceived low-grade fevers, and concern that the child did not recover. There often ensues another (clearly unrelated when thoughtfully reviewed in consultation) new febrile illness that is believed to be a continuation of the initial infection. This may occur several times, giving rise to a history that the child has had "continuous illness with fevers" for weeks to months exacerbating this misperception is a variety of factors, including absence of similar illness in siblings or classmates, association with significant constitutional symptoms (weight loss, extreme fatigue, and/or reduced activity) at the time of the first illness, inability to attend school or function at a previous level associated with the first febrile episode (often continuing during the extended period of "low-grade" fevers), history of remote febrile seizures or premature birth with a neonatal intensive care unit stay, other underlying concern for the health and well-being of the child prior to the illness (the vulnerable child syndrome), familial or other pressures undermining the parents' (and/or child's) confidence in the child's intrinsic health, and lack of confidence in the health care provider's diagnosis of "it's just a virus" [57].

5.4 Rare causes of PUO

Since 1961, there have been a variety of serological diagnostic tests helpful in the diagnosis of most

collagen vascular diseases. The result has been that collagen vascular diseases are a relatively uncommon cause of PUO at the present time. Rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are rare causes of PUO because of the many serological tests currently available to diagnose these disorders. The collagen vascular diseases that continue to be diagnostic problems, presenting as PUOs include those which are not readily diagnosable by simple or specific diagnostic tests. At the present time, collagen vascular diseases that are likely to remain undiagnosed after one month of fever and one week of inpatient/outpatient diagnostic testing include Kikuchi's disease, Takayasu's arteritis, late onset rheumatoid arthritis (LORA), polymyalgia rheumatica (PMR), temporal arteritis (TA), vasculitides, for example, periarteritis nodosa (PAN), and adult juvenile rheumatoid arthritis (JRA) also known as adult onset Still's disease [11].

It is believed that viral infections and the hyperimmune reaction due to these infections are involved in the etiology of Kikuchi-Fujimoto Disease (KFD), a rare cause of rheumatic/inflammatory PUO[81,82]. Kikuchi's disease is also known as histiocytic necrotizing lymphadenitis, a benign, self-limited disorder usually in middle-aged women of Asian descent. Although KFD was described more than 40 years ago, the etiology of this disease remains unsolved. It is hypothied to be caused by viral infection (Epstein–Barr virus (EBV), human herpesvirus (HHV) types 6, 7, and 8, herpes simplex virus, HIV, human T-lymphotrophic virus, and parvovirus B19, autoimmune disorders bring linked to SLE (precede or occur simultaneously), or genetic defect (upregulated genes included FI44L, CXCL10, GBP1, EPSTI1, and IFI27). The precise incidence of KFD is unknown; however, a large review identified and analyzed 733 patients diagnosed worldwide since 1972. Of those cases, 140 (19%) were pediatric patients, and the male:female ratio was 1.4:1.8 (It is worth noting that a higher propensity for male sex has only been observed in children younger than 12 years of age. The recurrence rate of KFD was approximately 4%-15%[82, 83].

Infectious or autoimmune processes were proposed but have not been definitively confirmed. It has seen recent increases in its prevalence in children [82]. Cervical adenopathy is typical and often accompanied by leukopenia. In middle-aged adults patients presenting with an PUO, the presence of otherwise unexplained cervical adenopathy should suggest the possibility of lymphoma or, rarely, Kikuchi's disease [84]. While extranodal involvement is rare, there have been reports of cases with presenting symptoms of skin lesions, arthritis, and, as with our case, aseptic meningitis and weight loss. No specific laboratory tests contribute to the diagnosis of KFD, though the most commonly reported laboratory findings seen in KFD are leukopenia, and elevated lactate dehydrogenase and ESR. Diagnosis is based on histopathological examination. Excisional lymph node biopsy is essential for a correct diagnosis. Apoptotic coagulation necrosis with karyorrhectic debris and the proliferation of histiocytes, plasmacytoid dendritic cells, and CD8(+) T cells in the absence of neutrophils are characteristic cytomorphology features. Interface dermatitis at the onset of KFD may be a marker for the subsequent evolution of SLE [82, 83].

In a study conducted by Kim *et al* in South Korea, 8 patients (8%) were diagnosed with necrotizing lymphadenitis and the frequency was increased compared with a previous study published 10 years earlier in Korea [71]. In patients with enlarged lymph nodes accompanied with fever, the possibility of necrotizing lymphadenitis should be considered [21]. Although KFD is rare among the pediatric population, this form of lymphadenitis should be considered in pediatric patients who present with prolonged fever or cervical lymphadenopathy of undetermined etiology. Given that the typical presentation of KFD is very similar to other disorders such as tuberculous lymphadenitis or malignant lymphoma, early diagnosis could possibly minimize costly and unnecessary evaluations and treatments. The natural course of the disease is typically benign. Short courses of steroids, nonsteroidal anti-inflammatory drugs, or hydroxychloroquine can be administered to patients with more severe symptoms [82].

Neoplastic disorders have now displaced infectious diseases as the most common cause of PUOs. Most neoplasms are associated with no or low-grade temperatures, with some important exceptions. Hypernephromas and lymphomas are neoplasms typically associated with high spiking fevers or may present as PUOs. Hematologic malignancies, that is, the acute and chronic leukemias, myeloproliferative disorders, and multiple myeloma, do not usually present with acute fevers or as PUOs. Multiple myeloma in elderly can present with PUO. Differential diagnostic possibilities in this patient included plasma cell leukemia, relapse of multiple myeloma, secondary/superimposed malignancy, or opportunistic infection. Naprosyn test remains a valuable diagnostic test to use to narrow differential diagnostic possibilities in patients with PUOs when a malignancy is a diagnostic consideration [85].

Schnitzler's syndrome and hyper-IgD syndrome are rare disorders that may present as PUOs. These entities should be suspected in patients on the basis of SPEP with obscure PUOs. An elevated IgM spike on SPEP is a clue to suspect Schnitzler's syndrome. A PUO patient with an IgD spike should suggest hyper-IgD syndrome, particularly if decreased IgA is also present [86].

Pseudolymphomas are drug induced and usually due to diphenyl hydantoin. In the PUO setting, pseudolymphomas present in the differential diagnosis of

adenopathy. The history of medications associated with pseudolymphomas is critical in suspecting the diagnosis. Obviously, lymphomas need to be ruled out before pseudolymphoma is considered as the cause of the patient's adenopathy [53].

5. 5 PUO in the Returning Traveler

The returning traveler with fever presents a diagnostic challenge for the health care provider. When evaluating such a patient, the highest priority should be given to diseases that are potentially fatal or may represent public health threats. A good history is paramount and needs to include destination, time and duration of travel, type of activity, onset of fever in relation to travel, associated comorbidities, and any associated symptoms. Pretravel immunizations and chemoprophylaxis may alter the natural course of disease and should be inquired about specifically. The fever patterns, presence of a rash or eschar, organomegaly, or neurologic findings are helpful physical findings. Laboratory abnormalities are nonspecific but when corroborated with clinical and epidemiologic data may offer a clue to diagnosis [87].

According to the GeoSentinel Surveillance Network and its database created between 1997 and 2006 based on 24,920 cases, 28% of returning travelers reported fever as a major reason for seeking medical care, similarly to 90% of travelers who were diagnosed with malaria, 82% with dengue, 87% with influenza, 96% with leptospirosis, 87% with enteric fever, 100% with measles, and 72% with rickettsial infections (spotted fever, murine typhus and scrub typhus) and Infectious mononucleosis; a disease mainly caused by EBV, but CMV, HIV or toxoplasmosis may also be responsible for causing mononucleosis- like diseases [88, 89]. In the GeoSentinel Surveillance Network survey, there are 10 regional classifications. A place of exposure turned out to be crucial in diagnosing returning travelers. Those who travelled to Sub-Saharan Africa and Oceania and reported fever as a chief symptom were most often diagnosed with malaria. Travelers coming back from South-East Asia and the Caribbean were more likely to be diagnosed with dengue. Ill travelers returning from South-Central Asia were most commonly diagnosed with enteric fever. Chikungunya was more likely among patients returning from Indian Ocean Islands. Those diagnosed with rickettsial diseases were usually coming back from Southern Africa. Most of them suffered from tick-borne rickettsioses. Dermatologic conditions were more likely among travelers to Oceania, South-East Asia, South and Central America and the Caribbean [89-91]. About 30% of the travelers with fever didn't seek pre-travel consultation, while 27% claimed to have sought medical advice. Pre-travel medical consultation was associated with noticeably lower morbidity for *P. falciparum* malaria. At the same time, patients who had had pre-travel consultation were less likely to get a severe illness [92]. Among noninfectious disorders are deep venous thrombosis and/or pulmonary emboli caused by venous stasis from inactivity during long aircraft flights [53].

When collecting history, a physician should take special interest in the patient's recent travels. He/she should ask about the visited countries as well as about the visited regions, as some pathogens can only be present in certain parts of a given country, e.g. in rural areas. A physician should inquire about exposure history: sexually transmitted diseases, food-borne illnesses, vector-borne infections; fever may also coexist with other illnesses or injuries (skin rashes, bites, burns). A physician should also consider cosmopolitan pathogens and common infections such as urinary tract infections and upper respiratory tract infections, and never assume that fever may only be travel-related. When in doubt, malaria should be ruled out first as it is the deadliest of the illnesses percurrent with fever. What is more, in one out of 3 cases, the cause of a fever in travelers returning from tropical destinations is malaria, for that reason diagnostic procedures undertaken by medical professionals should primarily be oriented towards identifying or eliminating this specific disease entity [92].

5. 6 Gossypiboma

Gossypiboma or retained surgical towels, are rare, but can cause important morbidity and mortality. Usually they are discovered during the first few days after surgery, but may remain undetected for many years. Bowel obstruction, perforation, pseudotumor or peritonitis are most often the clinical presentation, but in some cases only constitutional symptoms prevail. Diagnosis can be difficult, mostly because of low clinical suspicion. Lourenco and co-workers reported a case of a woman who presented with fever and weight loss three and half years after an abdominal surgery. After an extensive workup, a gossypiboma was finally discovered and removed, leading to a complete cure [93].

5.7 Factitious fever

It represents a large group of false illnesses varying from malingering to personality disorders. Patients tend to appear sick and seek medical advice by distorting their histories and physical findings and often laboratory tests. They tend to shift from hospital to hospital once the factitious nature of their illness is uncovered and often leave the hospital against medical advice. Chronic factitious illness is usually superimposed on a severe personality disorder varying from psychosis to neurosis. Factitious Fever is more common amongst medical and paramedical staff e.g. nurses, pharmacists, bacteriologist, laboratory technicians and medical students, because of their familiarity with the hospital, easy access to thermometers and drugs and because of the prompt attention given to them by their fellow members. Various methods of producing fraudulent fever are: thermometer manipulation, self inoculation of bacterial cultures, toxoids and milk,

drugs (Penicillins and sulphonamidesl barbiturates, phenytoin, procainamide, quinidine, atropine, propylthiouracil chlorpromazine, diphenyihydantoin and phenolphthalein). True factitious fever does not occur in children younger than 10 years of age because of their inability to manipulate with thermometers. Factitious Fever might complicate an existing or resolving disease. The physician must not neglect coexisting medical illness while treating factitious fever or self induced infection. Life threatening complications, e.g. bacterial endocarditis, or septic pulmonary emboli can often occur in self induced infections. Bacteremia should be treated spontaneously. Early psychiatric consultation should be a part of the investigation for any patient with prolonged illness with or without psychiatric signs and symptoms [94, 95].

5.8 Habitual Fever

Habitual fever, psychogenic fever or emotional pyrexia,is a condition of unknown cause that occurs in young females, characterized by mild body elevated temperatures of 99° F to 100.5° F regularly or intermittently for years, associated with fatigue, malaise, vague aches and pains, insomnia, bowel disturbances, and headaches. No organic cause can be found. In fact, psychiatric illnesses and emotional disturbances have been found to be associated with elevated body temperature due to disorder hypothalamic setup point. The diagnosis is usually made only after a prolonged period of study and observation. No specific treatment is recommended. Reassurance and psychotherapy offer the best relief.

5.9 PUO Due to Zoonoses

More than half of the 1407 human pathogens are zoonotic, making zoonotic infections an important subcategory in the PUO classifications. Brucellosis, leptospirosis, Q fever, Tularemia, rickettsioses and emerging viral zoonoses (Rift Valley, West Nile, Ebola, Nipah, Hendra, Marburg, and toga virus) are among the common and unusual zoonoses causing fevers of unknown origin. Simian immune virus is considered as a possible emerging infection. PUO Due to Zoonoses are of concern for special populations (the homeless, zoophiliacs, those whose occupation or leisure brings them in close contact with oceans or lakes, and veterinarians) [96].

5.10 PUO in solid organ transplant recipients

Worldwide, an estimated 119,873 solid organ transplants were performed in 2014 [97]. The positive effects of the immunosuppressive agents, obligatory for the prevention of organ rejection, have been tempered by the negative effects of these same therapies, leading to various infections that range in both frequency and severity. Other factors include induced antiproliferative activity of the immunosuppressive agents leading to mucosal erosions, transient cytopenia, uremia, hyperglycemia, malnutrition, use of invasive devices (leading to trauma, colonization, and infection), abnormalities in tissue perfusion (vascular or surgery-related etiologies). Donor-derived infections are of particular significance, as evidenced by several reports of infectious diseases transmitted through transplanted organs. They include viruses (hepatitis B and C, herpes viruses, human T-cell lymphotropic viruses (HTLV) 1 and 2, West Nile virus, rabies, LCMV, polyomavirus BK/JC, HPV, parvovirus B19, CMV, EBV (and PTLD), HIV), mycobacteria (tuberculous and nontuberculous mycobacteria), meningococcus, syphilis, parasites (malaria, Babesia, *Toxoplasma gondii*, *Trypanosoma cruzi* [Chagas disease], S stercoralis), and several fungal organisms. Donor-derived drug-resistant bacteria may also be transmitted, including vancomycin-resistant *enterococci*, MRSA, multidrug-resistant tuberculosis, vancomycin-resistant *enterococci*, *Clostridium difficile*, along with gram-negative healthcare-associated bacteria, play a significant role, especially in the postoperative period (<30 days post transplant)[98, 99], Drug-resistant infections and many others. Opportunistic pathogens such as *Legionella* and *Nocardia* remain a major challenge. These organisms are generally inhaled, establishing a pulmonary infection that may result in pneumonia or cavitary lesions, followed by dissemination to brain, bone, or skin. Listeria monocytogenes is yet another pathogen resulting in bacteremia, meningitis, and sepsis. Among fungal pathogens, the most common opportunistic fungi include Candida species, molds such as *Aspergillus*, and *Cryptococci* [100, 101].

5.11 PUO in HIV/AIDS patients

HIV-associated PUO is defined as recurrent fevers over a 4-week period in an outpatient setting or for 3 days in-hospital with HIV infection [4]. PUO constitutes a common clinical challenge in patients infected with HIV. Primary HIV infection can present with a mononucleosis-like syndrome in which fever is a prominent feature. It is usually caused by disseminated opportunistic infection, and the relative frequency of each cause of PUO is influenced by multiple factors including CD4 count usually < 100 cells/mm3, geographic setting, and local prevalence of infectious agents, which may provide clues to the diagnosis. In patients with a CD4 cell count over 200 cells/mm^3, the differential diagnosis and work-up is the same as for classic PUO, although the increased risk of tuberculosis and lymphoma must be taken into account. Infectious etiology predominates as the cause of HIV-associated PUO, accounting for 82.2% of cases in some studies [102]. Infections presenting as PUO in the HIV population occur most often in the late stages of the disease and high diagnostic suspicion for mycobacterial disease should be maintained when evaluating these patients, particularly in areas of high prevalence. Very low CD4 count predisposes the patient to *M. avium*-intracellulare and *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia. Late in course of HIV other causes include cytomegalovirus infection,

disseminated histo-plasmosis, and lymphoma. In contrast Mycobacterium tuberculosis and leishmaniasis are the most common causes of PUO in Europe. Parvovirus B19 should be considered if anemia is present. Certain diagnoses should be considered if the patient is from endemic areas or has traveled to endemic areas, such as the Ohio and Mississippi river valleys in the United States or in South America (*histoplasmosis*), southwest United States (*coccidioidomycosis*), Latin America (*Trypanosoma cruzi*), Southeast Asia (*Penicillium marneffei*), and Mediterranean basin and Latin America (leishmaniasis). Noninfectious causes of PUO in HIV patients include lymphomas, particularly non - Hodgkin's lymphoma, and drug fever. Because infection is the most common cause of PUO in HIV patients, the work-up should be pursued until the cause is revealed[53, 54, 103].

The introduction of HAART has led to a decline in the incidence of HIV-associated PUO. In a retrospective study performed in Spain between 1997 and 1999, among 4858 patients receiving HAART, the frequency of PUO was 0.6% as compared to 3% in 2787 patients not receiving HAART. In addition, HAART has resulted in unique manifestations of the same illnesses reported to cause PUO in the pre-HAART era [104].

Several studies have shown that adequate CD4 and viral load (VL) responses to HAART provide a clinical benefit by protecting against HIV disease progression [105-107]. In the evaluation of prolonged, unexplained fevers in HIV-infected patients, the patient's previous exposures, stage of HIV infection, and epidemiologic setting often provide important clues.

5.12 PUO in Malignancies

In developed countries malignancies have superseded infections as the most common cause of PUO[108]. In Petersdorf's classic paper on PUO, published in 1961, infectious diseases were the most common etiology of PUO, and neoplasms constituted the second most frequent category. This shift from infectious to malignant etiology as the most frequent cause of PUO is related to several factors. Firstly, due to the widespread introduction of computed tomography (CT) and magnetic resonance imaging (MRI), many intra-abdominal causes of infection are diagnosed early and therefore do not meet the definition of prolonged fever required to make the diagnosis of PUO. Secondly, radionucleotide imaging studies, that is, indium scans, gallium scans, and bone scans, have been useful in identifying occult malignancies undetectable by other means. Thirdly, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have helped to identify those cases of atrial myxoma presenting as PUO. Lastly, the population is aging, and malignancies are more common in the elderly population. The combination of these factors has resulted in malignancies becoming the most frequent overall cause of PUO in adults [109].

Most malignancies are not associated with fever as few malignancies are associated with acute or subacute fevers, and fewer yet are associated with prolonged fevers that may present as PUOs. Malignancies may cause fever directly or indirectly. Malignancies may cause fever indirectly by compression/obstruction of a hollow viscus, with subsequent infection and an increase in temperature due to the infectious component. Another way neoplasms cause fever indirectly is perforation of a hollow viscus. Perforation of an intra-abdominal viscus results in peritonitis, the severity of which is related to the size of the perforation and location in the gastrointestinal tract or pelvis [110]. Malignancies may cause fever directly via pyrogenic cytokine production (IL-1, IL-6, TNF, IFN) as seen in some patients with renal carcinomas, lymphomas, acute or chronic myeloid leukaemia's and soft tissues sarcomas. Infections elicit a different cytokine response than do neoplasms, that is, interleukins are released in infection, whereas tumor necrosis factor is the usual mechanism of fever from neoplasms. The fever generated by malignancies presenting as PUOs is either of the prolonged, low-grade variety or it may be a high-grade spiking fever that mimics infection [111].

Indirect causes of fever in malignancies can occur through the treatments used on the patients such as neutropenia, transfusion, invasive diagnostics, therapeutic splenectomy, increased fragility of anatomic barriers (radiation or chemotherapy mucositis) and implanted catheters. Febrile neutropenia is a syndrome commonly anticipated in patients receiving treatment for cancer. In 60% of cases and due to a blunted inflammatory reaction, it presents as PUO and constitutes a medical emergency because of the high mortality of occult gram-negative bacteremia that may be present. For the last three decades, its management has included the prompt administration of empiric antibacterial therapy, a tactic that resulted in a subsequent reduction in mortality. Challenges remain the administration of the most appropriate empiric treatment regimen adapted to the evolving and changing epidemiology of infections in neutropenic patients, the development of markers of early diagnosis of severe bacterial or fungal infections, the risk stratification of patients, the establishment of targeted empiric (pre-emptive) antifungal therapy criteria, and the containment of the antimicrobial resistance that compromises effective treatment efforts through effective antibiotic policies and implementation of infection control measures, especially hand hygiene. The need for targeted antimicrobial or antifungal prophylaxis and supportive strategies, such as the use of growth factors, awaits to be further clarified [112].

5.13 PUO in Cirrhosis

Fever in a cirrhotic patient is often a matter of great concern. Numerous diagnostic maneuvers, including cultures, blood tests, imaging studies, and, on occasion, invasive procedures are employed to ascertain the cause of fever. Patients with cirrhosis who have fever present a challenge to the physician. The literature is sparse about the differential diagnosis of fever in such patients. Cirrhotic fever could be defined as fever of undiagnosed etiology occurring in the patient with cirrhosis in the absence of an identified infection, malignancy, collagen vascular disease, alcoholic hepatitis, pancreatitis, tuberculosis, fungal infection, or drug fever. Fever attributed to cirrhosis is often low-grade, protracted, unaccompanied by focal signs and symptoms, and less likely to be associated with tachycardia and tachypnea than in patients with infections. Biliary cirrhosis and alcoholic cirrhosis tend to produce higher fevers [113].

The pathogenesis of fever of cirrhosis has not been fully elucidated. It may be related to hepatic necrosis or inflammation and to altered hepatic metabolism of steroids. Elevated levels of endotoxins and cytokines, for example, tumor necrosis factor-alpha (TNF-alpha), interleukin-1-beta (IL-1-beta), and interleukin-6 (IL-6), have also been demonstrated in patients with cirrhosis and may be involved in the pathogenesis of low-grade fever observed in cirrhosis [114].

Infectious complications in cirrhotic patients can cause severe morbidity and mortality. Bacterial infections are estimated to cause up to 25% of deaths in cirrhotic patients. The most frequent are urinary tract infection, spontaneous bacterial peritonitis, respiratory tract infection, and bacteremia [115]. The specific risk factors for infection in cirrhotic patients are low serum albumin, gastrointestinal bleeding, intensive care unit admission for any cause, and therapeutic endoscopy. Certain infectious agents are more virulent and more common in patients with liver disease. In adults, primary peritonitis has usually been reported in patients with cirrhosis and ascites [116]. The prevalence of primary peritonitis in hospitalized patients with cirrhosis and ascites has been estimated at 10% to 30%. In cirrhotic patients, micro-organisms presumably of enteric origin account for 69% of the pathogens. *Escherichia coli* is the most frequently recovered pathogen, followed by *Klebsiella pneumoniae*, *Streptococcus pneumonae* and other *streptococcal* species, including *enterococci*. Fever in cirrhotics is also noted with hyposplenic function due to the many organisms including *Streptococcus pneumoniae—Pneumococcus, Hemophilus influenza* type b (Hib), Meningococcemia caused by *Neisseria meningitides*, *Capnocytophagia canimorsus* or the DF-2, *Salmonella* species, *bartonellosis,* Babesiosis caused by *babesia microti*, Ehrlichiosis caused by *anaplasma phagocytophilum* [117].

5.14 Nosocomial PUO

Nosocomial PUO is defined as fever that started more than 72 hours after admission to an acute care hospital and persists without an obvious source of infection. The etiology of the fever in this category is usually nosocomial infections, followed by drug fever and thromboembolic diseases. Most infectious causes of fever can be diagnosed with the work-up described below. Other entities to keep in mind in the work-up include drug fever, drug withdrawal (alcohol, benzodiazepine, barbiturate, methadone), transfusion of blood products (red blood cells, platelets), granulocyte-stimulating factors, chemical phlebitis, pancreatitis, acute respiratory distress syndrome, acute myocardial infarction (especially in the first few days), Dressler's syndrome (in the later phase of acute myocardial infarction or after cardiac surgery), thyroid storm, acute adrenal insufficiency, and gout [54].

5.15 PUO in neutropenic patients

Neutropenic patients with PUO can be divided into 2 major categories: transplant patients and cancer patients on therapy presenting with febrile neutropenia. Febrile neutropenic patients who are undergoing chemotherapy are often seen in the emergency department, and it is critical to understand their management. The most accepted definition for febrile neutropenia for patients receiving chemotherapy is 1 temperature of at least 101°F or 2 episodes of 100.4°F more than 1 hour apart and an absolute neutrophil count less than 500. Although infections are the most common cause of fever in neutropenic patients (and therefore antibiotics should always be started empirically), other entities that should be entertained as possible etiologies include tumor-related fever, transfusion of blood products, and drug fever. Some medications that have been implicated in drug fever include bleomycin, cytosine arabinoside, and allopurinol [54].

5.16 Recurrent/Episodic PUO

Is probably the most perplexing and intriguing presentation that can be defined as a subtype of PUO meeting the classical criteria of PUO and characterized by at least two episodes of fever with fever free intervals of at least two weeks and seeming remission of underlying illness. This symptom free period varies in length and could extent to years. An interval of at least two week helps to exclude conditions that recur due to interruption or tapering of an inadequate empiric therapy. Typical example is infective endocarditis and non infectious inflammatory disorders treated with NSAID. This also can occur when fever subsides spontaneously, patients are reluctant for further investigations and physician are familiar with good prognosis of the condition they propose watchful waiting outpatient follow-up. Recurrent fever is a feature of some infectious diseases including epidemic typhus, trench fever, louse borne and tick borne relapsing fevers, and murine typhus [53]. Recurrent PUO is different from periodic fever

used to describe familial Mediterranean fever (FMF), a member of a group of disease of unknown origin known as periodic diseases and characterized with symptoms that recur with remarkable periodicity. It is suggested by a recurrent serositis/episcleritis with hypophyon in PUO patients with a positive family history of FMF [118-120]. Recurrent PUO many cases continue to evade a final diagnosis despite repeated assessment. It represents a subgroup of patients with very prolonged disease duration and it is known that the chance of reaching of diagnosis in cases with fever lasting more than 6 months is low. It may be caused by relapse of a partially treated disorder, by a disease with known course of spontaneous remission and relapses, or by repeated exposure to pyrogens, whether microorganisms or other substances, typical example of the later are extrinsic allergic alveolitis or hypersensitivity pneumonitis caused by inhalational allergens such as pigeon breeder's disease and drug fever due to repeated intake of medications (nitrofurantoins for UTI). Diseases with typical fluctuating course are Still's disease, relapsing polychondritis, Behcet's disease, mastocytosis and familial auto-inflammatory syndrome including FMF [53, 121].

Relatively few disorders are associated with a double quotidian fever, i.e., visceral leishmaniasis, mixed malarial infections, right-sided gonococcal acute bacterial endocarditis, and JRA. Cunha *et al*., reported a case with Recurrent PUO, Aseptic meningitis, hepatosplenomegaly, pericarditis and a double quotidian fever due to JRA. The only laboratory abnormalities in this patient included elevated serum transaminases, a mildly elevated erythrocyte sedimentation rate, a moderately elevated level of serum ferritin and double quotidian fever was present, which provided the key diagnostic clue in this case [121].

Similarly, benign neoplastic disorders may recur periodically and present as recurrent PUOs if the initial etiology of the fever is not initially determined. Fevers of malignant neoplasms are self-limiting naturally or with therapeutic interventions. Rheumatic inflammatory causes are, by nature, disorders that tend to periodicity with episodic exacerbations and remissions. Among all the categories of PUOs, rheumatic inflammatory diseases are the most likely to manifest as recurrent PUOs. Other miscellaneous causes of recurrent fever include cyclic neutropenia. Other PUOs prone to relapse include relapsing polychondritis, periapical dental abscesses, Crohn's disease, and alcoholic cirrhosis [53].

6. Approach to PUO

The differential diagnoses of PUO are extensive and require prompt and appropriate investigations. This mandates knowledge of many diseases across a range of clinical specialties, as well as knowledge of less commonly used investigative tools. As both the community and medicine continue to change, the aetiology and epidemiology of the diseases that cause PUO also change. For these reasons, it is important for physicians to approach PUO in a logical manner, and for the causes and approach to PUO to be continuously reviewed. Comprehensive clinical assessment is vital to provide diagnostic clues and tailor investigations. Moreover, evolving knowledge and the improvement in diagnostic methods, including new microbiological techniques and new instrumental procedures, necessitate a constant update of the tests included in a minimal diagnostic workup to qualify a fever as PUO[6, 55].

The mainstay of the clinical approach to the problem of the patient with PUO remains an analysis of the data derived from an accurate, complete detailed history of the present illness and physical examination and careful analysis of laboratory findings. Meticulous collection of such data should be the primary concern of the physician to guide the diagnostic workup and limit diagnostic possibilities towards the final diagnosis of PUO cases [122][53].

There is currently no standardized diagnostic approach for working up PUO. The general direction of the workup often depends on the patient's presentation, symptoms, and environmental exposures. It is generally accepted that a complete history and physical, basic laboratory tests, and empiric antibiotic therapy are initial steps in the workup of PUO [57].

The approach to PUO should pass through three phases.

- **Initial evaluation** should include a relevant PUO history as well as a physical examination that looks particularly for diagnostic findings relevant to PUO. Initial nonspecific laboratory tests also provide clues pointing toward a particular diagnosis while simultaneously eliminating other diagnoses from further consideration. The initial evaluation should narrow diagnostic possibilities and determine the direction of the subsequent diagnostic workup. A ''complete history'' and ''comprehensive physical examination.'' Should be stressed.
- **Focused evaluation** consists of a focused history, physical examination, and additional relevant nonspecific laboratory tests in patients who remain undiagnosed after the initial PUO evaluation. The focused PUO phase of diagnostic evaluation is based on a more detailed history that has PUO relevance. The PUO physical exam similarly concentrates on areas that have high diagnostic yield in PUO patients. Clinicians should be aware of the diagnostic significance of physical findings relevant to both infectious and noninfectious PUO disorders. Focused PUO laboratory testing is not specific, but is directed by the focused history and physical examination and leads to further diagnostic refinement.
- **PUO workup** is the definitive diagnostic testing, which incorporates specific laboratory testing or biopsy to confirm the diagnosis [53].

In PUO patients, there are almost always one or, more clues from the history and physical examination or nonspecific laboratory tests that suggest a disease category in general, or more specifically, a number of diagnostic possibilities. The diagnostic process to identify the cause of PUO should be guided by the PDCs. The diagnoses obtained in patients presenting PDCs were significantly higher than in patients without PDCs (72 vs. 30%, P=0.013). Only when no PDCs are found, or when the PDCs do not reveal the cause of PUO, a standardized step-to-step approach should be applied. All the PDCs that emerge from the standardized approach should be given credit [6].

A common error in the diagnostic approach to the PUO involves laboratory testing. All too often, undue relevance is placed on use of laboratory testing to arrive at a diagnosis. Not enough attention is paid to PUO historical details and physical examination. Among the misleading factors in the diagnostic approaches made by the physician; regarding the anamnesis (24.6%), the clinical examination (22.6%), the wrong interpretation of a laboratory test (20.7%), and inadequacy in the evaluation of a symptom and/or a positive test (5.6%).

1-Clinical perspective

Because PUOs are caused by such a wide variety of disorders, the diagnostic approach to the PUO patient is often extensive but is not focused or directed by the most likely diagnostic possibilities. A routine history and physical examination are inadequate in evaluating the PUO patient. It is a common misconception that extensive laboratory testing constitutes a comprehensive workup that will lead to the correct diagnosis in patients with PUO.

The initial PUO history should include:

- Place of birth (e.g., foreign-born)
- Prior/recent domicile (e.g., homelessness)
- Employment status and workplace conditions
- Recreational habits (e.g., alcohol, cigarettes, recreational drugs [including intravenous drugs])
- Hobbies (e.g., water sports, gardening, bird-watching)
- Recreational activities (hiking, sailing, swimming)
- Nutritional history (e.g., consumption of unpasteurized milk, dairy products, undercooked meat)
- Transfusion history
- Incarceration history
- Sexual history (e.g., current/former partners, barrier precautions, history of prior sexually transmitted diseases)
- Travel history, use of prophylactic anti-malarial medication and travel vaccinations
- Potential exposure to arthropod vectors (e.g., spelunking, hiking)
- Pets (e.g., dogs and cats [recent/remote bites], kittens [catscratch disease], reptiles [enteric infections], birds [e.g., psittacine exposures], exotic animals, including sources of acquisition)
- Contact with animals (zoonotic infections)
- Current medications (e.g., antacids, protein-pump inhibitors with risk of achlorhydria)
- Food or water exposures (potential for food-borne organisms/toxins)
- Comorbid illness that increases the risk of infection (egg, diabetes, chronic lung disease).

The physical examination should pay particular attention to the fundi, adenopathy, hepatic/splenic enlargement, heart murmur, and intra-abdominal or other masses. Repeated, careful and targeted physical examination may reveal physical signs missed on previous examinations. It is worth documenting a careful examination of the sinuses for tenderness, the oropharynx, fundi, skin and nails, thyroid gland, lymph nodes, external genitalia and rectum. All too frequently these are omitted from the physical examination or performed in a cursory way and important signs omitted. This can result in diagnostic delay and wasted resources performing unnecessary tests.

2- Laboratory investigations

There are many potential causes of PUO so it is not possible to list a standard battery of tests which should be performed to investigate every case. It is preferable to tailor the investigations according to clues which may have been suggested by the history and repeated physical examinations.

The diagnostic significance of nonspecific laboratory test abnormalities in the PUO workup is often missed if results are not considered together. Nonspecific laboratory abnormalities and clinical syndromic presentation, when taken together, may limit or eliminate various diagnoses from further diagnostic consideration and should be interpreted in the context of the PUO. Testing should be focused and directed by the differential diagnosis suggested by the focused PUO history and physical and nonspecific laboratory tests.

3-Focused diagnostic approach (Clinical syndromic approach)

Focused PUO laboratory tests add further refinement to the initial laboratory tests in limiting diagnostic possibilities. With PUO syndromic diagnosis, the pattern of organ involvement should be apparent from aspects of the history, physical examination, and laboratory tests. The pattern of organ involvement based on the focused PUO evaluation determines diagnostic possibilities for prompt and definitive diagnostic testing. The focused PUO workup should be detailed but directed as the most likely diagnosis, based on each disorder's pattern of organ involvement as determined by the focused PUO history, physical examination, and selected nonspecific laboratory tests [53]. After the initial and focused PUO evaluation of infectious disease causes, there are relatively few infections whose diagnosis remains elusive. These infections are not

rare or difficult to diagnose, but are missed in the initial and focused PUO evaluation (e.g., relapsing mastoiditis, chronic sinusitis, subacute bacterial osteomyelitis, periapical dental abscesses). These entities are readily diagnosed with appropriate imaging studies.

Physical findings relevant to rheumatic/inflammatory disorders require careful attention to the eyes, the fundi, neck, and the throat. Careful evaluation of adenopathy/splenomegaly and heart murmur is important. Clearly, joint swelling or effusion or arthritis is of paramount importance in this group.

Important aspects of the focused PUO history for neoplastic disorders include the careful evaluation of the past and family history of malignancies. Particular attention should be paid to the presence or absence of night sweats, pruritus after a hot bath or shower, and weight loss, particularly when accompanied by a dramatic decrease in appetite. Important aspects of the physical examination include abnormalities of the cranial nerves, the eyes (including the fundi), the throat, heart murmur, adenopathy, hepatosplenomegaly, sternal tenderness, and bone tenderness.

Miscellaneous disorders should be considered if the predominant clinical presentation does not point to an infectious, rheumatic/inflammatory, or neoplastic etiology. A relevant history for miscellaneous disorders includes medications or exposure to fumes. History of alcoholism should be included as well as thyroid/autoimmune disorders. Inquiries should be made regarding inflammatory bowel disease, particularly for extra intestinal complaints. In patients with a history of alcoholism/cirrhosis, physical examination for miscellaneous causes should focus on the myriad manifestations. Physical examination in patients with drug fevers is notable for the absence of physical findings. An exception is pseudolymphoma due to drugs (e.g., diphenylhidantoin). On physical examination, the findings related to subacute thyroiditis are related to the phase of the disease (i.e., the patient is most likely to be euthyroid or slightly hypothyroid when subacute thyroiditis presents as a PUO).

A diagnostic flow chart for PUO is presented in Figure 4. The flow chart proposes a homologation of the minimal diagnostic work-up to achieve a more standardized definition of PUO. Moreover, the proposed flow chart allows a rational approach to the several laboratory, instrumental and invasive methods used to reach a final diagnosis.

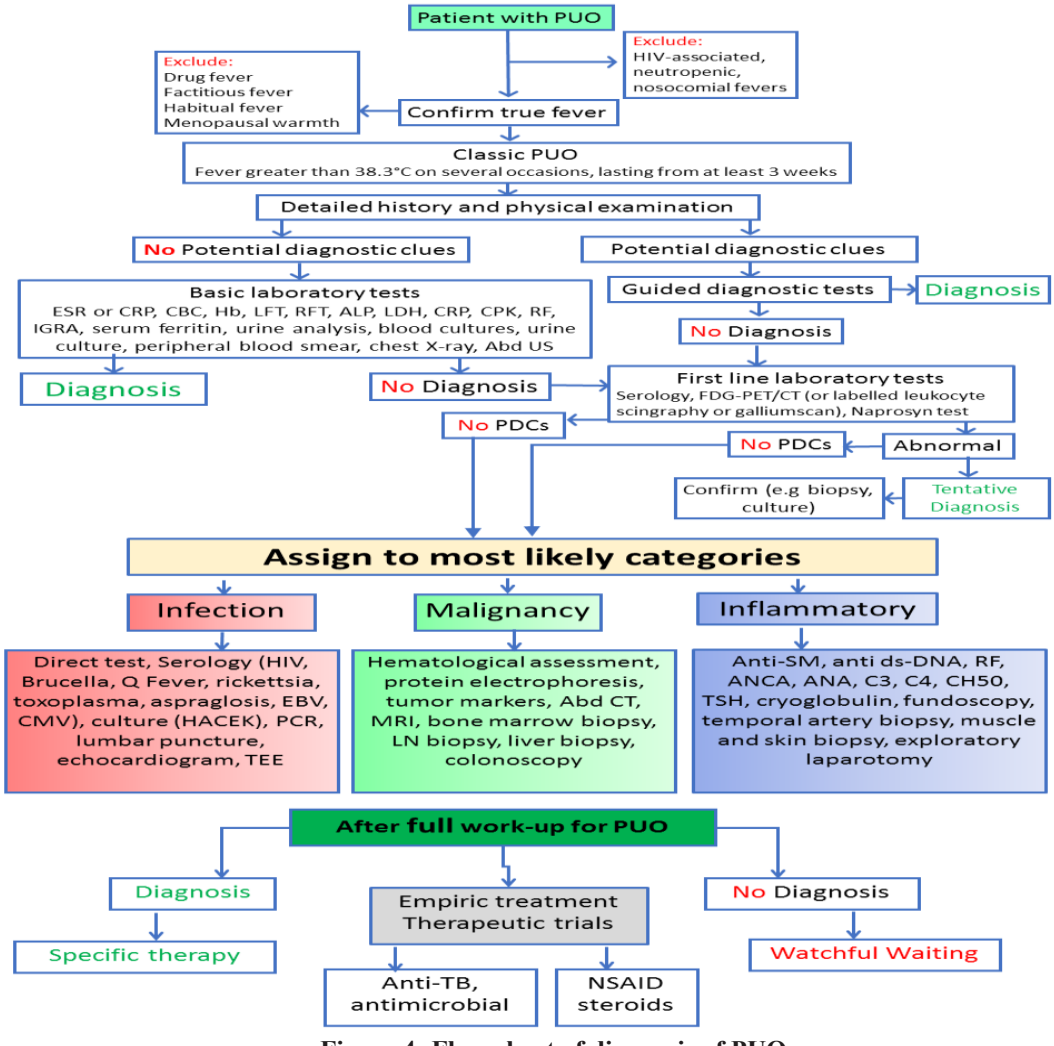

Figure 4: Flow chart of diagnosis of PUO

Based on the diagnosis of a child case of PUO with HLH disease, Antoon *et al*., proposes that a triad of laboratory tests, consisting of uric acid, LDH, and ferritin, should be performed for children if either the initial albumin is decreased or if fever remains despite the use of broad spectrum antibiotics [123]. They also recommended that uric acid, LDH, and ferritin be included in a basic evaluation consisting of a CBC, CMP, urinalysis, cultures, and chest X-ray. Ferritin is a well-known acute-phase reactant. An increased ferritin in the absence of iron overload is found in autoimmune, malignancy, and inflammatory diseases, such as HLH, juvenile idiopathic arthritis, systemic lupus erythematous, and acute lymphoblastic leukemia [124]. Furthermore, a serum ferritin greater than 10 000 μg/mL is 90% sensitive and 96% specific for HLH [125]. A ferritin level on initial evaluation would have helped exclude infectious causes and narrowed the differential significantly. Uric acid is a marker of cell turnover and aids in the diagnosis of various malignant and proliferative pediatric disorders [126]. LDH is a marker of tissue breakdown and hemolysis with abnormalities seen in malignancy, acute or chronic connective tissue disease, and certain infections, such as HIV, meningitis, and viral hepatitis [127]. Incorporating these simple and inexpensive lab tests may improve time to diagnosis and proper treatment in any of these disease states (Figure 5). This may also aid in early diagnosis of other PUO etiologies where workup is delayed while common infectious causes are ruled out. Decrease the time to diagnosis and treatment in those with serious and life-threatening disease that present with PUO, thus decreasing unnecessary tests and lowering health costs [123].

One of the most underutilized test in PUO patients is serum ferritin levels. Elevations of serum ferritin levels are often ignored or explained away as being due to ferritin acting as an “acute phase reactant”. In a patient with PUO, by definition, the process is no longer acute, and elevations in the serum ferritin level take on a very different significance. Serum ferritin is also important in diagnosing neoplastic diseases [11]. An elevated ferritin level in prolonged febrile illness may indicate malignancy (especially myeloproliferative disorders) and other noninfectious inflammatory diseases, such as JRA, SLE or temporal arteritis [128]. Its levels of patients in the infectious disease were found significantly lower than those of patients in the neoplasm and collagen vascular disease, while serum procalcitonin (PCT) levels in the infectious disease was higher than that in the neoplasm and collagen vascular diseases. Serum ferritin and PCT may be useful in discriminating infectious from non-infectious causes (neoplasms and collagen vascular diseases) in patients with PUO [58].

Elevated lactate dehydrogenase levels can be indicative of infectious and malignant causes of PUO, including malaria, lymphoma, and leukemia. Measurement of ferritin levels may also be helpful. Clinicians should also consider malignancy, renal disease, and inflammatory disorders if the ESR is 100 mm per hour or greater [128].

The Naprosyn (naproxen) test, which was first developed by Chang, uses Naprosyn, a nonsteroidal anti-inflammatory drug (NSAID), to differentiate neoplastic from infectious causes of fever. This test is useful to further define the diagnostic workup so that diagnostic efforts may be focused on determining a neoplastic or infectious etiology have little or no decrease in temperature during the test period, whereas those with neoplasms have a prompt and dramatic decrease in temperature for all or most of the 3-day test period. The Naprosyn test works with neoplasms that generate fevers from the malignancy itself (not an associated complication of malignancy). Although there is less experience with other NSAIDs, it appears that other NSAIDs have no effect on infectious fevers while having inhibitory effect on neoplastic fevers. As with other tests, the Naprosyn test should not be applied in situations where its use has not been defined [85, 129].

The more nonspecific- test-abnormalities present in a PUO patient, the more likely it is that a specific diagnosis will be suggested. For example, in a patient with an elevated ferritin level and an ESR >100 mm/hr the differential is large and primarily related to neoplasms, but primarily restricted to the general categories of malignancy and collagen vascular disease. The value of the nonspecific tests mentioned is enhanced when combined with other history and physical examination findings to further direct the diagnostic work up in the PUO patients. Nonspecific tests are often helpful in suggesting an otherwise unsuspected diagnosis and are useful in eliminating entire diagnostic categories from further consideration. If, in addition to an elevated serum ferritin level and a highly elevated sedimentation rate, the patient also has basophilia, then collagen vascular diseases are eliminated and the diagnosis is in the general category of a neoplasm [53].

All disorders have a specific pattern of organ involvement. The pattern of organ involvement, in turn, determines the history, physical findings, and nonspecific laboratory abnormalities associated with various diseases. In a patient with PUO, there are almost always one or more clues from the history, physical examination, or nonspecific laboratory tests that suggest a particular diagnosis or at least limit diagnostic possibilities. The main difficulty with diagnostic testing in patients with PUO is that it is unfocused. The greatest errors in PUO workup relating to the diagnostic evaluation are related to over testing and under testing. Ordering tests that have no potential clinical usefulness is wasteful and unnecessary. Alternately, too few diagnostic tests, particularly those are necessary and appropriate, not relevant to the clinical setting, prolong a misdirected diagnostic PUO workup. The key to the

diagnostic approach with PUOs is a focused and complete clinically relevant workup. Using a focused approach, physicians can arrive at a definitive diagnosis more quickly, less expensively, and less invasively than using the "shotgun" approach to order every available test [53].

7. Role of New diagnostics

Procalcitonin is a newer marker specific for bacterial infection. In multiple studies, procalcitonin has been shown to have a specificity ranging from 70% to 98%, with a higher specificity for bacterial infection than other markers. It may be helpful in distinguishing between fevers with a bacterial cause vs. noninfectious inflammatory diseases, but its role in the workup of PUO is currently undefined [128].

Sequencing of the 16s ribosomal RNA (rRNA) gene is new diagnostic technique that has been successfully used for bacterial identification in culture negative samples where there is a clinical suspicion of microbial involvement. The 16s rRNA sequencing has higher culture rate of bacteria than traditional culture methods and novel species can be detected12).

PET-CT has been used in some studies for the diagnosis and management of PUO, owing to its ability to assess the morphology and functional characteristics of the tissues simultaneously [130]. FDG-PET is based on the increased uptake of FDG (fluorodeoxyglucose) by activated inflammatory cells, which occurs in infection, NIID and malignancy due to their higher rates of glycolysis. This technique allows the matching of inflammatory lesions with a precise anatomical location. It is also useful in staging and follow-up of certain malignancies. It was reported that the estimated diagnostic accuracy, sensitivity and specificity of PET-CT for PUO were 90.5%, 93.8% and 80%, respectively with high positive predictive value 93% and negative predictive value (100%). A hybrid of CT and 18F fluorodeoxyglucose positron emission tomography has a higher diagnostic yield (sensitivity of 56% to 100%; specificity of 75% to 81% [128,130,131]. However, PET-CT has several disadvantages include high radiation doses, relatively high cost, limited availability, high rate of false-positive results and its inability to detect systemic, non-focal disease. Although PET-CT can be used as a valuable tool for evaluation of certain cases of PUO, clinicians should consider both advantages and disadvantages of PET-CT and use this modality in limited situations [21, 131]. The diagnostic yield of CT alone is lower than the yield of FDGPET/ CT. This is partly because specific anatomical changes may be absent in inflammation, particularly early in the illness, and CT cannot distinguish active infection from residual anatomical changes. Labeled leukocyte scintigraphy or gallium scintigraphy can be used as alternatives when FDG-PET/CT is unavailable, but have lower diagnostic yield and lower uptake and clearance [128, 130-132].

All of viruses were detected by culture till 2008 before PCR was available. Currently, multiplex respiratory virus PCR, which allows us to diagnose any respiratory viruses within 24–48 hours. Therefore, the number of patients with PUO caused by respiratory virus infection is expected to decrease over time.

Since malignancy is the main cause of death in PUO patients, early diagnosis is important to reduce mortality. Therefore, appropriate imaging studies or early invasive procedures such as bone marrow examination should be performed in certain patients with suspicious presentation for malignancies.

An initial approach in the evaluation of PUO in HIV-infected persons should be to discontinue medications, especially certain antiviral agents (such as abacavir) and sulfa agents. Accompanying clinical features of opportunistic infections causing prolonged fever often overlap with those associated with drug reactions cytopenias, elevation of liver enzyme tests. If there is no response after two to three days, blood cultures is a good method of identifying the causative organisms. Tuberculin skin testing and antigen testing for H. capsulatum in serum and urine also should be performed. A dilated ophthalmologic examination should be performed to investigate retinitis due to cytomegalovirus [133].

PUO is still a challenging medical problem. Infections remain the most common cause in Egypt, confirming the trends found in other parts of the world, followed by connective tissue diseases and finally neoplasm. A keen clinical eye, meticulous history taking with repeated physical examinations and simple logistic laboratory tests are the most important diagnostic tools. Daily physical examination while the patient is hospitalized is essential. Special attention should be paid to rashes, new or changing cardiac murmurs, arthritis, abdominal tenderness or rigidity, lymph node enlargement and neurologic deficits. This was the cornerstone upon which the laboratory workup should be designed.

8. Management of PUO

The treatment of PUO is guided by the final diagnosis, but when no cause is found, antipyretic drugs can be prescribed. Corticosteroids should be avoided in the absence of a diagnosis, especially at an early stage. The prognosis of PUO is determined by the underlying cause. The majority of patients with unexplained PUO will eventually show spontaneous remission of fever. Treatment is very important for patients with HLH, as the condition is life-threatening. The treatments that doctors use suppress the immune system. Patients are usually treated with steroids plus chemotherapy (etoposide / VP-16) and / or an antibody therapy that destroys the T cells (called anti-

thymocyte globulin or ATG). Patients may receive other medications that suppress the immune system. Additionally, medications that help treat any infections that are present, or that prevent new infections from occurring can be given. Alternatively, many patients may require bone marrow transplantation.

8.1 Disease-modifying treatment

In considering treatment of PUO, the concern is essentially with symptomatic treatment because, by definition, the underlying disease is unknown. Specific disease-modifying treatment can usually be commenced only once the diagnosis has been established. The exception is when empirical drug therapy is used as an attempt to confirm or refute a suspected diagnosis. Giving empirical antibiotic therapy for a patient with a PUO is usually not appropriate. If the fever responds without a specific diagnosis being established, there is a risk that an important condition such as endocarditis may be missed. This may result in a potentially adverse outcome in that the endocarditis is suppressed but not cured and the patient subsequently relapses. Empirical therapy with antituberculosis drugs can be used as a therapeutic trial if extrapulmonary tuberculosis (TB) appears likely, but there is little potential for obtaining a positive mycobacterial culture. However, if rifampicin is included among the empirical anti-TB drugs it must be remembered that this antibiotic could suppress fever in many other conditions including brucellosis and osteomyelitis. Therefore, many clinicians omit rifampicin from therapeutic trials of anti-TB drugs.

8.2 Symptomatic treatment

There are two important issues to take into account when considering symptomatic treatment:

1 Will the symptomatic treatment mask the clinical signs and thus hinder diagnosis?

2 Could the symptomatic treatment affect the prognosis of any of the potential differential diagnoses?

Antipyretic drugs are frequently overprescribed in patients with fevers, particularly among inpatients with recent onset of fever. The masking of temperature by paracetamol and non-steroidal drugs can lead to the erroneous conclusion that a patient is recovering. Therefore, fever in hospitalized patients should usually be treated only if it poses a threat to the patient or is causing substantial discomfort. Treatment of fever is less likely to obscure the diagnosis in patients with an established PUO than in hospital inpatients with recent symptoms. This is both because the established fever is unlikely to subside completely and because the longer duration of symptoms means that apparent short-term resolution of fever should be interpreted with caution. Historically, the pattern of fever has been said to correlate with specific conditions, but this is rarely diagnostically useful in the individual patient (except perhaps in malaria). Antipyretic drugs are unlikely to affect the prognosis of conditions causing PUO, so it is not unreasonable to give them to patients with PUO if they are suffering discomfort, particularly if they are being investigated as outpatients. If corticosteroids are used as a therapeutic trial, they may mask symptoms (e.g. rashes and fever). If the patient has an underlying haematological malignancy, steroids may potentially adversely affect future treatment response. Thus, if a therapeutic trial of steroids is being considered for a suspected CTD such as temporal arteritis or polymyalgia rheumatica, the clinician needs to be certain that the patient does not have an occult lymphoma or other malignancy [68].

With many PUOs, patients and physicians frequently attempt to lower the patient's fever. Fever is a cardinal sign that serves as the impetus to determine a diagnosis in both acute fevers and PUOs. Decreasing the temperature may make the patient feel better, but it does not answer the fundamental question of what is causing the patient's prolonged elevated temperatures Suppression of fever serves no physiologic or clinical purpose a part from making the patient feel better, but it does not answer the fundamental question of what is causing the patient's prolonged elevated temperatures. Antipyretics should be avoided because they obscure the febrile response and alter fever patterns that may be thus eliminating important diagnostic clues as fever pattern curves and the relationship of pulse to temperature, often resulting in a more difficult or delayed diagnosis [134]. In some situations, empiric therapy in patients with PUOs is reasonable and necessary. The approach to PUO of awaiting diagnosis before considering treatment is suggested as the mortality of PUO is low, and early use of antipyretics or antimicrobials may delay diagnosis. The mortality rate for PUO is less than 10%, with most deaths occurring as a result of malignancy. The empiric treatment of true culture-negative endocarditis is reasonable if the patient meets the previously discussed criteria for culture negative endocarditis provided that the patient shows peripheral manifestations of endocarditis. Empiric therapy for temporal arteritis is vital and may prevent permanent blindness. Vasculitic doses of corticosteroids should be used in the treatment of such patients. If military TB is suspected and the patient is deteriorating clinically, empiric anti-TB therapy is reasonable and may be life-saving. Miliary TB is a difficult diagnosis to confirm and requires biopsy of liver or bone marrow. Biopsy results take time, and patients deteriorating with potential miliary TB should be given empiric trial of anti-tuberculous therapy at least until biopsy results are available to rule out or confirm the diagnosis of miliary TB. Most other infectious diseases presenting as PUOs (e.g., Q fever, SBE) are usually not rapidly progressive, and appropriate therapy can be initiated after the diagnosis is confirmed serologically or by PCR. With these few exceptions, empiric treatment of PUOs should be avoided,

and efforts should be directed at arriving at a definitive diagnosis [53]. Also for suspected cases of Polymyalgia Rheumatica, low-dose steroids may confirm the diagnosis. If temporal arteritis is suspected and visual symptoms appear, it is critical that high-dose steroids be given to prevent blindness [135].

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