Presentation of infection in older patients—a prospective study

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**Background.** Traditional wisdom suggests that infections in older patients have atypical presentation, including blunted febrile response. Data are scarce. **Design.** We analyzed data from a prospectively collected database on presentation of infection in 4,308 patients, and compared the presentation of older patients (≥ 75 years) versus adults (<75 years). **Settings.** Single tertiary medical center. **Participants.** Patients admitted with suspected bacterial infection during 2002–2004 and 2010–2011. **Measurements.** We evaluated clinical presentation on day of admission, including vital signs and laboratory parameters. **Results.** No difference in fever values as a presenting sign of infection was found between older patients and adults (median fever 38.3°C, interquartile range [IQR] 37.4–39.0°C; and 38.4°C, IQR 37.3–39.0°C, respectively, P = 0.08). Median leukocyte count was significantly higher in older patients (median 11.60, IQR 8.30–15.72 in older patients; 10.84, 7.50–15.00 in adults, P < 0.001). Presentation with septic shock, acute renal failure, and reduced consciousness was significantly more common in older patients. These findings were also consistent in the subgroups of bacteremic patients and patients with microbiologically documented infection. **Conclusion.** Elevated fever and leukocytosis were found to be at least equally common in older patients compared to younger adults as part of the presentation of infection.

**Key words:** Elderly, geriatrics, infection presentation

Infections are an important cause of morbidity and mortality among the older patients. Influenza and pneumonia, for example, represent the seventh leading cause of death among US adults aged 65 years or older (1).

Certain infections occur more often in the older patients, including urinary tract infection and pneumonia (2,3). Increase in the incidence of sepsis with increasing age has also been documented (4,5), with increased mortality (6).

Multiple explanations for the increased rate of infections among older patients have been suggested, including co-morbid illnesses, exposure to instrumentation and procedures, institutionalization, immunosenescence, malnutrition, and poor performance status (5). Higher morbidity and mortality due to infections in older patients compared to younger patients have been attributed in part to the diagnostic challenge in this population (3,7).

The traditional wisdom is that presentation of infection in older patients is different than in younger patients and that older patients tend to have fewer symptoms (3), e.g. fever may be absent or blunted in 20%–30% of older patients with serious infection (8). In addition, non-specific manifestations such as falls, altered mental status, anorexia, urinary incontinence, or generalized weakness are considered common and often only presenting signs of infection (2,3,5).

Data of these observations are scarce. Clinical studies comparing infection presentation in older patients versus younger patients are few and most of them small and retrospective (9–16). Most of them report lower rates of fever and leukocytosis as presenting signs in older patients, and higher rates of altered mental status and renal failure. The question whether bacterial infections may have atypical presentations in older patients is of utmost importance: it dictates the threshold for starting antibiotics in old people with atypical presentations, and drives antibiotic consumption and resistance.

We aimed to assess differences in infection presentation between patients ≥ 75 years old versus < 75 years old, hospitalized with suspected bacterial infection or in whom infections should have been suspected and included in a prospectively collected database.
Methods

Patients
We analyzed a database of patients from Rabin Medical Center, Beilinson Campus in Israel, collected from six departments of internal medicine (240 beds). Patients were enrolled as part of a three-phase study (two observational and one interventional) designed to evaluate the effectiveness of TREAT, a decision support system for antibiotic treatment of common bacterial infections in medical inpatients. Data were collected between June and December 2002, May and November 2004, and between May 2010 and April 2011. The local research ethics committee approved the study protocol.

Inclusion and exclusion criteria
We included all patients fulfilling systemic inflammatory response syndrome diagnostic criteria (17); patients with a focus of infection; patients with shock compatible with septic shock; patients with febrile neutropenia; patients prescribed antibiotics (not for prophylaxis); and patients from whom blood cultures were drawn, regardless of whether the suspected infection was acquired in the community or in the hospital.

We excluded human immunodeficiency virus-positive patients; solid-organ or bone-marrow transplant recipients; children aged less than 18 years; those with suspected travel infections or tuberculosis; and pregnant women. Patients fulfilling inclusion criteria were prospectively identified by daily chart review. Data collected at infection presentation included: demographic details; background conditions; predisposing conditions for infection and devices; general and focal signs and symptoms; and routine laboratory data. Data concerning use of beta-blockers are missing.

Definitions
We compare adults (age 18–74 years) to older patients (age 75 years or older). Fever was defined as any measurement of ≥ 38°C on the day of inclusion, and hypothermia as any measurement of < 36°C on the day of inclusion. Leukocytosis was defined as white blood cells (WBC) ≥ 12,000 cells/μL and leukopenia as ≤ 4,000 cells/μL.

Septic shock was defined as systolic blood pressure < 90 mmHg.

Acute renal failure was defined as a rise in serum creatinine of > 0.5 mg/dL if the baseline creatinine was < 2 mg/dL; and > 1 mg/dL if the baseline was > 2 mg/dL.

Microbiologically documented infection (MDI) was defined as an infection with a pathogen defined by a positive culture or a determination of an antigen or positive serology or PCR deemed as significant (and not contamination or colonization) by consensus of two clinicians.

Statistical analysis
Proportions were compared using the chi-square test, and continuous variables were compared using the Mann–Whitney U test (as most variables did not have a normal distribution). Analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA).

Results
Overall 4,308 patients were included: 2,375 adults and 1,933 older patients.

Fever
The median fever in older patients (2,269 patients) was 38.3°C (interquartile range [IQR] 37.4–39.0) and in adults (1,906 patients) 38.4°C (IQR 37.3–39.0) (P = 0.080). A significantly higher percentage of older patients (1.3%) had hypothermia (fever < 36°C) compared to adults (0.4%), but the number of patients presenting with hypothermia was low (24/1,906 older patients and 9/2,269 adults, P = 0.002). There was no significant difference in the percentage of patients with normal temperature on presentation (< 38°C and ≥ 36°C) between older patients (31.7% of patients) and adults (32.2% of patients) (P = 0.716). There was also no significant difference in the percentage of patients with high temperature (≥ 38°C) on presentation between older patients and adults (67.1% of older patients and 67.7% of adults, P = 0.818).

Heart rate and blood pressure (Table I)
There was a significant difference in the distribution of heart rate and blood pressure between age groups, with lower heart rate (HR) and diastolic blood pressure (DBP) and higher systolic blood pressure (SBP) in the older patients group. Data concerning use of beta-blockers are missing.

Other parameters assessed on presentation (Table I)
Normal level of consciousness was significantly less common in older patients (54.6% of older patients compared with 85.2% of adults) (P < 0.001). Parameters significantly more common in older patients were presentation with dyspnea, septic shock, and acute renal failure. On the other hand, chills (P < 0.001) and vomiting (P = 0.001) were significantly more common in adults.

Analyzing separately patients with abnormal consciousness at presentation demonstrated elevated fever, leukocytosis, or septic shock in 89.6% of older patients and 86.5% of adults. Among patients with abnormal consciousness, but with normal fever and leukocytes, and no septic shock only 19.1% of older patients and 16.7% of adults had microbiologically documented infection.

Laboratory values (Table II)
Comparisons of laboratory values are presented in Table II. In summary, median values of leukocytes, creatinine, urea, glucose, and sodium were all significantly higher in older patients, while median platelet counts were lower.

A significantly higher percentage of older patients had leukocytosis on presentation (885/1,845 [48.0%] of older patients and 940/2,198 [42.8%] of adults, P = 0.001).

Altogether 87 of 1,845 older patients (4.7%) presented with leukopenia compared with 210 of 2,198 adults (9.6%) (P < 0.001).

No difference was found in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) between older patients and adults. Lactate levels were significantly higher in older patients and albumin significantly lower. These data were available, however, for less than 50% of patients.

Subgroup of bacteremic patients (469 patients, Table I)
In the subgroup of bacteremic patients (236 elderly and 233 adults), no significant difference was demonstrated between older patients and adults in the distribution of fever, SBP, and DBP. Heart rate was significantly lower in the older patients (P < 0.001). Among bacteremic older patients, 11.3% presented with septic shock compared with 4.6% of bacteremic adults (P = 0.010).

Normal conscious state on presentation was significantly more common among bacteremic adults (77.5%) compared with bacteremic older patients (50.9%) (P < 0.001).

Among older bacteremic patients, 38.7% presented with acute renal failure, compared with 18.6% of bacteremic adults (P < 0.001).
Table I. Vital signs and other presenting signs and symptoms in older patients versus adults.

| Parameter            | Older patients | Adults | Difference | Older patients | Adults | Difference | Older patients | Adults | Difference | Bacteremia |
|----------------------|---------------|--------|------------|---------------|--------|------------|---------------|--------|------------|------------|
|                      | Median (IQR)  | Median (IQR) | P  | Median (IQR) | Median (IQR) | P  | Median (IQR) | Median (IQR) | P  | Median (IQR) | Median (IQR) | P  |
| Fever                | 38.3 (37.4–39.0) | 38.4 (37.3–39.0) | 0.08 | 38.7 (38.0–39.1) | 38.7 (38.0–39.4) | 0.458 | 38.5 (38.0–39.0) | 38.5 (37.9–39.1) | 0.843 |
| HR                   | 90.0 (80.0–109.0) | 95.0 (78.0–100.0) | <0.001 | 91.0 (80.0–106.0) | 101.0 (89.5–116.0) | <0.001 | 90.0 (80.0–103.0) | 100.0 (86.0–110.7) | <0.001 |
| SBP                  | 126.0 (108.0–145.0) | 120.0 (105.0–138.0) | <0.001 | 120.0 (100.0–138.0) | 114.0 (98.0–137.0) | 0.288 | 122.5 (105.0–142.0) | 117.0 (102.0–138.0) | 0.012 |
| DBP                  | 67.0 (58.0–77.0) | 70.0 (61.0–79.0) | <0.001 | 63.0 (52.0–75.0) | 64.0 (56.0–75.0) | 0.191 | 65.5 (55.0–75.2) | 67.0 (58.0–77.0) | 0.047 |

| Parameter            | n (%)       | n (%) | P       | n (%)       | n (%) | P       | n (%)       | n (%) | P       |
|----------------------|-------------|--------|---------|-------------|--------|---------|-------------|--------|---------|
| Consciousness        | 1029 (54.6) | 1898 (85.2) | <0.001 | 117 (50.9)  | 172 (77.5) | <0.001 | 218 (45.6) | 384 (78.5) | <0.001 |
| Dyspnea              | 608 (35.8) | 462 (22.3) | <0.001 | 58 (27.9)  | 40 (19.7)  | 0.052 | 127 (29.4) | 101 (22.3) | 0.016 |
| Septic shock         | 81 (4.4)   | 59 (2.7)   | 0.03 | 25 (11.3)  | 10 (4.6)   | 0.01 | 39 (8.4)   | 19 (3.9)   | 0.004 |
| Acute renal failure  | 388 (21.1) | 241 (11.2) | <0.001 | 86 (38.7)  | 41 (18.6)  | <0.001 | 141 (30.5) | 82 (16.9)  | <0.001 |
| Chills               | 257 (16.7) | 458 (23.5) | <0.001 | 68 (34.9)  | 73 (37.4)  | 0.598 | 100 (25.4) | 141 (33.3) | 0.014 |
| Vomiting             | 177 (9.3)  | 292 (12.6) | <0.001 | 21 (9.1)   | 35 (15.3)  | 0.041 | 46 (9.5)   | 65 (12.9)  | 0.091 |

DBP = diastolic blood pressure; HR = heart rate; IQR = interquartile range; SBP = systolic blood pressure.

Table II. Laboratory values in older patients versus adults.

| Value                  | Older patients | Adults | Difference | Older patients | Adults | Difference | Older patients | Adults | Difference | Bacteremia |
|------------------------|---------------|--------|------------|---------------|--------|------------|---------------|--------|------------|------------|
| Leukocytes (×10^3/microL) | 11.6 (8.3–15.7) | 10.8 (7.5–15.0) | <0.001 | 12.8 (8.7–18.0) | 11.0 (7.9–15.5) | 0.018 | 12.6 (8.8–16.9) | 11.4 (7.8–15.5) | 0.001 |
| Creatinine (mg/dl)     | 1.1 (0.8–1.6)  | 0.9 (0.7–1.2)  | <0.001 | 1.3 (0.9–2.0)  | 1.0 (0.7–1.4)  | <0.001 | 1.2 (0.9–1.7)  | 0.9 (0.7–1.3)  | <0.001 |
| Urea (mg/dl)           | 55.0 (39.0–85.0) | 55.0 (24.0–54.0) | <0.001 | 66.5 (47.0–105.3) | 46.0 (29.0–70.0) | <0.001 | 60.0 (43.0–98.0) | 40.0 (27.0–66.0) | <0.001 |
| Glucose (mg/dl)        | 130.0 (108.0–177.0) | 118.0 (99.0–157.0) | <0.001 | 129.0 (106.0–176.0) | 123.0 (102.0–181.5) | 0.533 | 130.0 (107.0–181.0) | 124.0 (102.0–176.0) | 0.106 |
| Sodium (mmol/L)        | 137.0 (133.0–140.0) | 136.0 (133.0–139.0) | 0.001 | 136.0 (132.0–138.5) | 134.0 (132.0–138.0) | 0.023 | 136.0 (133.0–139.0) | 136.0 (133.0–138.0) | 0.051 |
| Platelets (>10^3/microL) | 228.0 (167.5–310.0) | 237.0 (176.0–315.0) | 0.019 | 202.0 (144.8–267.0) | 208.0 (137.0–287.0) | 0.665 | 225.0 (167.0–307.0) | 224.0 (157.3–299.8) | 0.369 |
No difference between bacteremic adults and older patients was demonstrated in rates of chills (73/195 [37.4%] adults, 68/195 [34.9%] older patients, \( P = 0.598 \)) or dyspnea (40/203 [19.7%] adults, 58/208 [27.9%] older patients), although the latter had a trend for higher rates in older patients (\( P = 0.052 \)).

Differences in laboratory values among bacteremic patients are presented in Table II. In general, median values of leukocytes, creatinine, urea, glucose, and sodium were significantly higher in older patients, while median platelet count was lower.

A significantly higher percentage of bacteremic older patients had leukocytosis on presentation (123/226 [54.4%] of older patients and 92/222 [41.4%] of adults, \( P = 0.006 \)).

Subgroup of patients with MDI (1,005 patients, Table I)

In the subgroup of patients with MDI (494 elderly and 511 adults), no significant difference was demonstrated between older patients and adults in the distribution of fever, SBP, and DBP. Heart rate was significantly lower in older patients with MDI (\( P < 0.001 \)).

Among patients with MDI, normal consciousness was a significantly more common presentation in adults (78.5%) compared with older patients (45.6%) (\( P < 0.001 \)). Chills were also more common in adults (33.3%) compared with older patients (25.4%) (\( P = 0.014 \)). Septic shock at presentation was significantly more common in older patients with MDI (8.4%) compared with adults with MDI (3.9%) (\( P = 0.004 \)), and so were dyspnea (\( P = 0.016 \)) and acute renal failure (\( P < 0.001 \)).

Differences in laboratory values among patients with MDI are presented in Table II. In summary, median values of leukocytes, creatinine, and urea were significantly higher in older patients, while no significant difference was demonstrated for median values of platelets, glucose, and sodium.

Categories of final diagnosis—entire cohort

The main categories of final diagnosis are described in Table III. Generally, lower respiratory and urinary tract infections were significantly more common among older patients (\( P < 0.001 \) for each diagnosis). Among adults, neutropenic fever (\( P = 0.001 \)), abdominal infections (\( P < 0.001 \)), and non-bacterial infections (\( P < 0.001 \)) were significantly more common.

No difference in rates of non-infectious causes was demonstrated between adults and older patients (\( P = 0.505 \)).

Discussion

We used data from a prospectively collected database to compare presentation of infection between adult patients (age < 75 years) and older patients (age ≥ 75 years). No significant difference in the distribution of fever was demonstrated between groups among all patients, bacteremic patients, and MDI patients. No significant difference was found in the percentage of patients presenting with elevated fever. Hypothermia at presentation was significantly more common in older patients compared with adults, but overall it was a rare presentation (1.3% of older patients).

Heart rate was consistently lower in older patients among all groups analyzed, but data concerning use of beta-blockers, which may explain this observation, are missing. Systolic blood pressure was higher and diastolic blood pressure was lower in older patients in the entire cohort, but not in the bacteremia or MDI subgroups.

Data from all patients and from the analyzed subgroups showed higher rates of presentation with abnormal consciousness, dyspnea, septic shock, and acute renal failure among older patients. Chills and vomiting were more common in adults.

Significantly higher median values of leukocytes, creatinine, and urea were measured in older patients in all the groups assessed. Median glucose and sodium values were higher in older patients in the entire cohort and among bacteremic elderly, and platelet levels were significantly lower.

Several earlier clinical studies reported lower rates of fever and leukocytosis as presenting signs in older patients (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1019915), and higher rates of altered mental status and renal failure (10,11,13–15). In a recent retrospective study (18) no significant difference was demonstrated in rates of fever ≥ 38.5°C between bacteremic adults and older patients. Chassagne et al. in their prospective study (9) did not find a significant difference in the frequency of fever or hypothermia between adults and older patients (>65 years). Reports on hypothermia in previous studies are also variable, including studies reporting no difference between older patients and adults (9,11), higher rates in older patients (10,12), and higher rates in adults (19).

Several studies have found lower baseline core temperature in older people (19–22). Others suggested blunted hypothalamic pathways for fever elevation in older people (23) and lower amplitude of circadian-rhythm temperature fluctuations (24). In a retrospective study a considerable number of patients presented without elevated absolute fever, but had a significant change from baseline (19). Our data suggest no clinical difference in fever as the presenting sign of infection in older patients versus adults.

Concerning leukocytosis or leukopenia on presentation, some previous studies report no difference between adults and older patients (9,18), while others report higher rates of leukocytosis (11) or lower rates of leukopenia (10) in older patients.

Several other methods have been assessed for diagnosing infection in the elderly, including measurements of CRP, procalcitonin (25,26), and volume conductivity scatter parameters of leukocytes (27). All the above parameters were found to have variable sensitivity. Median CRP levels in our study were similar between older patients and adults. It should be emphasized that, in older patients with abnormal consciousness but no traditional signs of infection, rates of true MDI were low.

Our study limitations are missing data on several parameters of infection, including CRP, lactate, and albumin, and on use of beta-blockers.

Our study was probably biased towards showing less fever or other sepsis signs in older patients, because the overall cohort was defined by physician’s clinical suspicion.

Possible limitations may be differences in baseline characteristics between older people and adults (e.g. as for lower baseline
temperature in older people, suggested above). However, previous studies described no difference in leukocytes and platelet values between older patients and younger patients (28,29). Some studies described elevated urea levels with advanced age, but most studies did not find a relation between age and creatinine levels (29). Serum creatinine may remain stable with age despite decreases in the glomerular filtration rate (30).

In conclusion, in our analysis of a large prospective database, elevated fever and leukocytosis were found to be as common in older patients as in adults as part of the presentation of infection. It should be emphasized that, in older patients with abnormal consciousness but no traditional signs of infection, rates of true MDI were very low. Our findings of typical presentation in older patients, including elevated fever and leukocytosis, may help in avoiding unnecessary use of antibiotics in older patients presenting without these signs.

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Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/07853890.2015.1019915.