Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults

Kristen L. Nowak,* Traci M. Bartz,† Lorien Dalrymple,‡ Ian H. de Boer,§ Bryan Kestenbaum,§ Michael G. Shlipak,‖¶** Pranav S. Garimella,†† Joachim H. Ix,‡‡§§‖‖ and Michel Chonchol*

*Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado; †Department of Biostatistics and §Division of Nephrology and Kidney Research Institute, University of Washington, Seattle, Washington; ‡Department of Medicine, University of California, Davis, Sacramento, California; Departments of ‖Medicine and ¶Epidemiology and Biostatistics, University of California, San Francisco, California; **General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, San Francisco, California; ††Division of Nephrology, Tufts Medical Center, Boston, Massachusetts; Divisions of ‡‡Nephrology and §§Preventative Medicine, University of California, San Diego, California; and ‖‖Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, California

ABSTRACT

Within monocytes, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] is important for production of cathelicidins, which in turn, are critical for antibacterial action. Fibroblast growth factor 23 (FGF23) decreases 1,25$(OH)_2$D production and thus, could increase infection risk. We examined this possibility in 3141 community-dwelling adults ages ≥65 years old at baseline in the Cardiovascular Health Study using Cox proportional hazards models to examine the association between FGF23 concentrations and first infection-related hospitalizations and determine whether associations differed by the presence of CKD (eGFR<60 ml/min per 1.73 m^2 [*n*=832] or urine albumin-to-creatinine ratio >30 mg/g [*n*=577]). Mean±SD age of participants was 78±5 years old, 60% of participants were women, and the median plasma FGF23 concentration was 70 (interquartile range, 53–99) relative units per milliliter. In fully adjusted models, higher FGF23 concentrations associated with higher risk of first infection-related hospitalization (hazard ratio [HR], 1.11; 95% confidence interval [95% CI], 1.03 to 1.20 per doubling of FGF23) during a median follow-up of 8.6 years. In participants with or without CKD (defined by eGFR), FGF23 concentration associated with first infection-related hospitalization with HRs of 1.24 (95% CI, 1.08 to 1.42) and 1.06 (95% CI, 0.97 to 1.17) per doubling of FGF23, respectively (*P*=0.13 for interaction). Associations did not differ between groups when stratified by urine albumin-to-creatinine ratio. In sensitivity analyses, the addition of serum calcium, phosphorus, 25-hydroxyvitamin D, intact parathyroid hormone, and 24,25-dihydroxyvitamin D did not meaningfully change the estimates. In conclusion, in community-dwelling older adults, higher plasma FGF23 concentrations independently associated with the risk of first infection-related hospitalization.

J Am Soc Nephrol 28: 1239–1246, 2017. doi: 10.1681/ASN.2016040401

Fibroblast growth factor 23 (FGF23) is a protein synthesized by osteocytes and osteoblasts that acts as a phosphaturic factor. It also suppresses renal synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] by inhibiting expression of the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1).[1,2] Numerous epidemiologic studies have shown high circulating FGF23 concentrations to be independently associated with adverse outcomes, including mortality and cardiovascular events, particularly among individuals with CKD, who have very high FGF23 circulating concentrations.[3–6]

Older adults account for a disproportionate amount of infection-related hospitalizations in the United States, and this number continues to

Received April 5, 2016. Accepted September 24, 2016.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Kristen L. Nowak, Division of Renal Diseases and Hypertension, University of Colorado at Denver Anschutz Medical Campus, 12700 East 19th Avenue C281, Aurora, CO 80045. Email: Kristen.Nowak@ucdenver.edu

rise.[7,8] Additionally, even moderate degrees of decreased kidney function are associated with a clinically significant increase in risk of infection-related hospitalization.[9] Higher FGF23 concentrations are associated with increased risk of infection in patients on chronic hemodialysis[10]; however, to our knowledge, similar associations have not been previously evaluated in older adults without ESRD.

FGF23 has recently been identified as a regulator of innate immunity and has been shown to suppress CYP27B1 in PBMC monocytes from healthy humans similar to its inhibition of CYP27B1 in the kidney, decreasing intracrine production of $1,25(OH)_2D$, concomitant with suppressed production of antibacterial cathelicidins.[11] Similarly, FGF23 treatment in peritoneal dialysate monocyte effluents from uremic patients decreases mRNA expression of CYP27B1.[11] Additionally, recent evidence showed that elevated FGF23 levels in the setting of CKD limit leukocyte recruitment and impair host defense.[12]

The purpose of this study was to determine the association of plasma FGF23 concentrations with first infection-related hospitalization in older community-dwelling adults. Additionally, we sought to determine whether this association was modified by the presence of CKD. We hypothesized that higher circulating FGF23 concentrations would be independently associated with first infection-related hospitalization and that the association would be stronger in individuals with CKD.

RESULTS

Participant Characteristics at Baseline

Among the 3141 study participants, the mean±SD age was 78±5 years old, 60% (n=1885) were women, and 16% (n=507) were black. The mean±SD eGFR was 70.8±19.4 ml/min per 1.73 m^2, and the median urine albumin-to-creatinine ratio (ACR) was 8.7 (interquartile range [IQR], 4.69–20.37) mg/g. Thirty-six percent had CKD (eGFR<60 ml/min per 1.73 m^2 [n=832] and/or urine ACR >30 mg/g [n=577]). The median plasma FGF23 concentration was 70 (IQR, 53–99) relative units per milliliter.

Compared with participants in the lowest FGF23 quartile, those with higher concentrations were older, more frequently women, less likely to be black, and had higher prevalence of chronic diseases, lower eGFR, higher urine ACR, and higher systemic inflammatory markers. Individuals with higher FGF23 concentrations also had higher serum calcium, phosphorus, and intact parathyroid hormone (iPTH) concentrations, whereas 25-hydroxyvitamin D [25(OH)D], 24,25-dihydroxyvitamin D [$24,25(OH)_2D$], and the vitamin D metabolic ratio [VMR; $24,25(OH)_2D$-to-25(OH)D ratio] concentrations were similar across FGF23 quartiles (Table 1).

First Infection-Related Hospitalization

During a median follow-up of 8.6 years (maximum of 17.1 years), 1164 participants (37%) had an infection-related hospitalization. The incidence rate for first infection-related hospitalization was the greatest for the highest quartile of FGF23 concentrations (5.8 infection-related hospitalizations per 100 person-years) (Table 2). Across all quartiles of FGF23 concentrations, the incidence rates for first infection-related hospitalization were greater for participants with eGFR<60 ml/min per 1.73 m^2 (quartile 4 incidence rate: 7.4 infection-related hospitalizations per 100 person-years) than those with eGFR≥60 ml/min per 1.73 m^2 (quartile 4 incidence rate: 4.8 infection-related hospitalizations per 100 person-years).

Relation between FGF23 and First Infection-Related Hospitalization

In analysis adjusted for age, race, and sex (model 1), higher plasma FGF23 concentrations were associated with a higher risk of first infection-related hospitalization (Table 3). This association was attenuated but remained significant after additional adjustment for smoking status, body mass index (BMI), diabetes, congestive heart failure (CHF), coronary heart disease (CHD), eGFR, and urine ACR (model 2). After additional adjustment for albumin, c-reactive protein (CRP), and IL-6 (model 3), the plasma FGF23 concentrations in the highest quartile (compared with the lowest quartile) were associated with a 26% greater risk of first infection-related hospitalization (95% confidence interval [95% CI], 5% to 53%). Similar results were obtained when FGF23 was modeled continuously (hazard ratio [HR] per doubling of FGF23, 1.11; 95% CI, 1.03 to 1.20).

To explore any differential associations of FGF23 with first infection-related hospitalization in patients with and without CKD, we performed the same analysis after stratification by CKD status using two different stratification variables (eGFR<60 and ≥60 ml/min per 1.73 m^2 and urine ACR ≤30 and >30 mg/g) (Table 4). The P values for the FGF23 × eGFR and FGF23 × urine ACR interaction terms were 0.13 and 0.58, respectively. In the final model, the point estimates for first infection-related hospitalization were qualitatively stronger in the subset with eGFR<60 ml/min per 1.73 m^2 than in those with higher eGFR. Each doubling in FGF23 was associated with 24% higher risk of infection-related hospitalization in individuals with eGFR<60 ml/min per 1.73 m^2 (95% CI, 8% to 42%) compared with a nonsignificant 6% higher risk in those with higher eGFR (95% CI, 3% lower to 17% higher). In contrast, associations of FGF23 with infection hospitalization were similar irrespective of albuminuria status. Additional *post hoc* analyses showed no group differences when stratified by the presence of diabetes, CHF, and CHD (Supplemental Table 1) (P values for interaction terms are P=0.52, P=0.82, and P=0.60, respectively).

In secondary analysis using a negative binomial regression, there was no significant association of FGF23 with number of infection-related hospitalizations (entire cohort [model 3]: HR per doubling of FGF23, 1.06; 95% CI, 0.98 to 1.15). When the Cox proportional hazards analysis was limited to only first hospitalization due to bacterial infections or infections considered likely be bacterial in origin, the estimate of association

Table 1. Demographic characteristics and laboratory measurements by quartile of FGF23

Variable	Quartile 1 <53.34 RU/ml, *n*=786	Quartile 2 =53.34–70.34 RU/ml, *n*=785	Quartile 3 =70.35–99.33 RU/ml, *n*=786	Quartile 4 >99.33 RU/ml, *n*=784	*P* Value (for Trend)
Age, yr	77±5	77±5	78±4	79±5	<0.001
Men, *n* (%)	369 (47%)	343 (44%)	281 (36%)	263 (34%)	<0.001
Black race, *n* (%)	181 (23%)	121 (15%)	98 (13%)	107 (14%)	<0.001
Smoking status, *n* (%)					0.002
Never	335 (43%)	324 (41%)	308 (39%)	303 (39%)	
Former	411 (52%)	411 (52%)	399 (51%)	404 (52%)	
Current	40 (5%)	50 (6%)	79 (10%)	77 (10%)	
Diabetes, *n* (%)	104 (13%)	129 (16%)	138 (18%)	199 (25%)	<0.001
CHF, *n* (%)	23 (3%)	44 (6%)	57 (7%)	156 (20%)	<0.001
CHD, *n* (%)	144 (18%)	161 (21%)	188 (24%)	261 (33%)	<0.001
BMI, kg/m^2	26.3±4.3	26.6±4.1	27.3±4.8	27.6±5.3	<0.001
eGFR, ml/min per 1.73 m^2	80.8±18.1	74.4±16.7	69.3±16.2	58.6±19.4	<0.001
ACR, mg/g	6.9 [4.3–14.3]	8.4 [4.5–17.3]	8.3 [4.7–19.0]	13.5 [6.1–54.0]	<0.001
Albumin, g/dl	3.80±0.30	3.81±0.30	3.78±0.29	3.76±0.30	<0.01
CRP, mg/L	4.08±9.38	4.19±7.25	4.97±6.60	5.64±8.24	<0.001
IL-6, pg/ml	3.1±2.1	3.4±2.3	3.9±2.5	4.6±2.7	<0.001
Calcium, mg/dl	9.70±0.53	9.79±0.58	9.78±0.55	9.81±0.64	0.02
Phosphorus, mg/dl	3.70±0.53	3.72±0.51	3.79±0.57	3.95±0.56	<0.001
25(OH)D, ng/ml	27.8±10.3	29.0±11.2	29.4±12.6	27.6±11.4	>0.99
iPTH, pg/ml	43.7±18.2	45.8±21.2	47.1±21.8	62.9±51.9	<0.001
24,25(OH)$_2$D, ng/ml	3.4±1.8	3.6±1.8	3.5±1.9	3.2±1.8	0.22
VMR	0.121±0.040	0.124±0.040	0.120±0.042	0.116±0.042	0.08

Data are mean±SD, *n* (%), or median [IQR]. eGFR was calculated by the cystatin C equation. Data are from a subgroup with a random sample of *n*=881 participants for the following variables: calcium, phosphorus, 25(OH)D, iPTH, 24,25(OH)$_2$D, and VMR. RU, relative unit.

with FGF23 remained similar (model 3: HR per doubling of FGF23, 1.13; 95% CI, 1.05 to 1.22).

Last, we conducted sensitivity analyses in 881 participants randomly selected for other mineral metabolism measurements. Results were similar after additional adjustment for circulating 25(OH)D, iPTH, calcium, phosphorus, and 24,24(OH)$_2$D or VMR (Table 5).

DISCUSSION

In ambulatory, community-dwelling older adults, higher plasma FGF23 concentrations were independently associated with the risk of first infection-related hospitalization. To our knowledge, this is the first study examining the association of FGF23 with infectious outcomes in older adults without ESRD, and it is of potential clinical relevance. Infection-related hospitalizations are associated with significant mortality and have a major economic effect on health care spending.[8] In older adults, hospitalization attributable to infectious disease is substantial and continues to rise over time[7,8]; persons with CKD have both increased complications and longer lengths of stay.[13] Reduced kidney function, even moderately, is associated with a linear increase in risk of first infection-related hospitalization.[9] Importantly, the mechanisms contributing to this risk are incompletely understood.[14] Measurement of FGF23 may provide new insights into risk of infection in community-living older adults and patients with kidney function decline.

To the best of our knowledge, only one other study has examined the association between FGF23 and infectious outcomes, and that study was in a population of patients on chronic hemodialysis.[10] In that study, higher circulating FGF23 concentrations were independently associated with higher risk of infection as defined by time to first infectious hospitalization or infectious death. Finding a similar association in a population of community-dwelling older adults is a novel observation, may provide new insights to mechanisms contributing to infection risk in older persons, and may ultimately have treatment implications for individuals at high risk of infection.

The mechanisms that may link increased circulating FGF23 with infection are incompletely understood. As was also the case in the recent study in patients on chronic hemodialysis,[10] inflammation did not seem to be an important mechanism, because adjustment for CRP and IL-6 did not significantly attenuate this association; however, these measurements were temporally separated from the outcomes and may have increased at the time of infection-related hospitalization. In sensitivity analyses further adjusted for other markers of mineral metabolism, the association was also unchanged. Although we did not assess the independent association of 25(OH)D with first infection-related hospitalization, it has been previously shown that higher circulating 25(OH)D

Table 2. Incidence rates of first infection-related hospitalization by FGF23 quartile for the overall cohort and stratified by eGFR

FGF23	No. of Events	Person-yr	Rate per 100 person-yr
Overall Cohort			
Quartile 1: <53.34 RU/ml (*n*=786)	266	79.6	3.3
Quartile 2: 53.34–70.34 RU/ml (*n*=785)	293	75.1	3.9
Quartile 3: 70.34–99.33 RU/ml (*n*=786)	297	71.2	4.2
Quartile 4: >99.33 RU/ml (*n*=784)	308	52.7	5.8
eGFR≥60 ml/min per 1.73 m^2			
Quartile 1: <53.34 RU/ml (*n*=720)	244	74.1	3.3
Quartile 2: 53.34–70.34 RU/ml (*n*=639)	233	62.9	3.7
Quartile 3: 70.34–99.33 RU/ml (*n*=570)	209	55.7	3.8
Quartile 4: >99.33 RU/ml (*n*=380)	153	31.7	4.8
eGFR<60 ml/min per 1.73 m^2			
Quartile 1: <53.34 RU/ml (*n*=66)	22	5.5	4.0
Quartile 2: 53.34–70.34 RU/ml (*n*=146)	60	12.3	4.9
Quartile 3: 70.34–99.33 RU/ml (*n*=216)	80	15.5	5.7
Quartile 4: >99.33 RU/ml (*n*=404)	155	21.0	7.4

RU, relative unit.

concentrations are associated with decreased risk of infection in patients on chronic hemodialysis[10] and community-dwelling adults.[15] However, it is possible that circulating markers of mineral metabolism do not reflect local $1,25(OH)_2D$ production, and these pathways may still mediate the association of FGF23 with first infection-related hospitalization, consistent with evidence that FGF23 reduces $1,25(OH)_2D$ production locally in monocytes.[11] Because FGF23 inhibits conversion of 25(OH)D to $1,25(OH)_2D$ by CYP27B1, elevated FGF23 may still predispose older adults to infection risk, even in the presence of adequate 25(OH)D. Thus, administering active vitamin D in older adults experiencing infection may have beneficial effects and is a compelling hypothesis for future research.

CYP27B1 and the vitamin D receptor are expressed in immune cells, and $1,25(OH)_2D$ may have autocrine or paracrine roles.[16] In response to binding of bacterial wall LPS, CYP27B1 and the vitamin D receptor expression are upregulated, increasing conversion of 25(OH)D to $1,25(OH)_2D$. This subsequently increases transcription of cathelicidins, bactericidal proteins that are particularly dependent on sufficient circulating 25(OH)D.[17,18] FGF23 has been shown to decrease CYP27B1 expression in monocytic cells, decreasing production of $1,25(OH)_2D$, concomitant with suppression of antibacterial cathelicidins.[11] The association with FGF23 was similar when a subanalysis was performed including only bacterial infections or infections considered likely to be bacterial in origin, consistent with a potential role of FGF23 in the transcription of cathelicidins. Recent evidence indicates that FGF23 may also directly impair neutrophil recruitment and host defense in the setting of CKD by interfering with leukocyte integrin activation and recruitment.[12]

Although the test for interaction was not statistically significant, the association of FGF23 with first infection-related hospitalization was qualitatively stronger by comparison of point estimates in participants with CKD as defined by eGFR<60 ml/min per 1.73 m^2. Other studies have also shown a stronger association of FGF23 with adverse outcomes in patients with CKD.[3,19] FGF23 may be particularly harmful in CKD by limiting conversion of 25(OH)D to $1,25(OH)_2D$.[20] Alternatively, it has been proposed that high FGF23 may mark a novel axis of kidney dysfunction, providing information about dimensions beyond those obtained by eGFR or urine ACR.[3] It is unclear why a moderate effect modification was seen on the basis of eGFR but not by urine ACR categories, but this may be due to the fact that albuminuria is measuring an earlier stage of kidney disease or reflects the ability of the kidney to maintain mineral metabolism homeostasis less. Thus, these results for first infection-related hospitalization differ from the association between FGF23 and both all-cause mortality and cardiovascular events, in which results were found to be stronger in individuals with CKD defined by either eGFR<60 ml/min per 1.73 m^2 or a urine ACR ≥30 mg/g.[3] Of note, little is known regarding the association of proteinuria with risk of infection as well as the risk of infection in general in nondialysis-dependent CKD.[14]

There was a significant association of FGF23 with first infection-related hospitalization using Cox proportional hazards analysis but not with number of infection-related

Table 3. Associations (HRs and 95% CIs) of FGF23 with first infection-related hospitalization

Model	Quartile 1 <53.34 RU/ml, *n*=786	Quartile 2 =53.34–70.34 RU/ml, *n*=785	Quartile 3 =70.35–99.33 RU/ml, *n*=786	Quartile 4 >99.33 RU/ml, *n*=784	Per Doubling of FGF23
Model 1	Reference	1.20 (1.01 to 1.41)	1.28 (1.08 to 1.51)	1.88 (1.58 to 2.22)	1.30 (1.22 to 1.39)
Model 2	Reference	1.08 (0.92 to 1.28)	1.07 (0.90 to 1.28)	1.31 (1.09 to 1.58)	1.14 (1.06 to 1.22)
Model 3	Reference	1.08 (0.91 to 1.28)	1.05 (0.88 to 1.25)	1.26 (1.05 to 1.53)	1.11 (1.03 to 1.20)

Model 1: age, race, and sex. Model 2: model 1, smoking status, BMI, diabetes, CHD, CHF, eGFR (cystatin C equation), and urine ACR. Model 3: model 2, albumin, CRP, and IL-6. RU, relative unit.

Table 4. Associations (HRs and 95% CIs) of FGF23 with first infection-related hospitalization stratified by kidney disease status (eGFR and urine ACR)

Model	Quartile 1 <53.34 RU/ml, *n*=786	Quartile 2 =53.34–70.34 RU/ml, *n*=785	Quartile 3 =70.35–99.33 RU/ml, *n*=786	Quartile 4 >99.33 RU/ml, *n*=784	Per Doubling of FGF23
eGFR≥60 ml/min per 1.73 m^2					
Model 1	Reference	1.15 (0.96 to 1.38)	1.18 (0.98 to 1.42)	1.58 (1.29 to 1.94)	1.19 (1.09 to 1.29)
Model 2	Reference	1.05 (0.87 to 1.26)	1.03 (0.85 to 1.25)	1.25 (1.01 to 1.55)	1.09 (0.99 to 1.19)
Model 3	Reference	1.04 (0.87 to 1.25)	0.99 (0.82 to 1.21)	1.19 (0.96 to 1.49)	1.06 (0.97 to 1.17)
eGFR<60 ml/min per 1.73 m^2					
Model 1	Reference	1.34 (0.82 to 2.19)	1.54 (0.96 to 2.46)	2.14 (1.35 to 3.40)	1.42 (1.26 to 1.59)
Model 2	Reference	1.31 (0.80 to 2.16)	1.31 (0.81 to 2.11)	1.59 (0.98 to 2.58)	1.26 (1.10 to 1.44)
Model 3	Reference	1.35 (0.82 to 2.22)	1.33 (0.82 to 2.16)	1.62 (1.00 to 2.64)	1.24 (1.08 to 1.42)
ACR≤30 mg/g					
Model 1	Reference	1.13 (0.94 to 1.36)	1.26 (1.05 to 1.50)	1.61 (1.32 to 1.95)	1.23 (1.13 to 1.33)
Model 2	Reference	1.06 (0.88 to 1.27)	1.12 (0.93 to 1.35)	1.28 (1.04 to 1.57)	1.12 (1.03 to 1.23)
Model 3	Reference	1.05 (0.88 to 1.26)	1.09 (0.91 to 1.32)	1.24 (1.00 to 1.53)	1.11 (1.02 to 1.21)
ACR>30 mg/g					
Model 1	Reference	1.38 (0.88 to 2.16)	1.24 (0.78 to 1.96)	2.16 (1.42 to 3.30)	1.37 (1.21 to 1.54)
Model 2	Reference	1.22 (0.77 to 1.92)	0.86 (0.53 to 1.40)	1.33 (0.82 to 2.15)	1.17 (1.00 to 1.36)
Model 3	Reference	1.19 (0.75 to 1.88)	0.82 (0.50 to 1.35)	1.24 (0.76 to 2.02)	1.13 (0.96 to 1.32)

Model 1: age, race, and sex. Model 2: model 1, smoking status, BMI, diabetes, CHD, CHF, eGFR (cystatin C equation), and urine ACR. Model 3: model 2, albumin, CRP, and IL-6. RU, relative unit.

hospitalizations using a negative binomial regression; the latter method measures the rate of infection (*i.e.,* number of infections per person-time), whereas Cox regression assesses the hazard rate of first infection. Thus, because there was longer person-time follow-up when using the negative binomial regression model, there was more attenuation of the association due to length of time between the baseline measurement of FGF23 and the outcome of interest. Additionally, the difference may be explained by the fact that FGF23 levels may be important for first infectious event but less so for later events, perhaps because prior infection may be a more important risk factor for subsequent infections.

There are several important limitations to this study. Because of the nature of the analysis, the results are observational only. Future studies should confirm these findings and test whether supplementation with $1,25(OH)_2D$ may decrease infection rates in older adults with elevated FGF23 concentrations. We adjusted for several important covariates, but the results may be subject to residual confounding. Whether residual confounding by severity of kidney function may influence this association requires future study and confirmation in other settings. We hypothesize that FGF23 may be related to infection-related hospitalizations by influencing $1,25(OH)_2D$ production within monocytes. With available data within the Cardiovascular Health Study (CHS), we were not able to test monocyte $1,25(OH)_2D$ production on the basis of FGF23 concentrations, and we did not have systemic $1,25(OH)_2D$ or cathelicidin concentrations available due to limited sample volume. However, $24,25(OH)_2D$ levels and VMR were measured as novel markers of vitamin D activity and adequacy and indirect markers of $1,25(OH)_2D$; $24,25(OH)_2D$ is the most abundant product of vitamin D catabolism. Because 24-hydroxylase is directly induced by $1,25(OH)_2D$, lower serum levels of $24,25(OH)_2D$ indicate diminished vitamin D activity,[21,22] and VMR reflects vitamin D adequacy.[23] Additionally, the findings may not apply to populations of younger adults, and International Classification of Diseases,

Table 5. Associations (HRs and 95% CIs) of FGF23 with first infection-related hospitalization for the 881 participants in a random subgroup with measurements of markers of mineral metabolism

Model	Quartile 1 <53.34 RU/ml, *n*=223	Quartile 2 =53.34–70.34 RU/ml, *n*=228	Quartile 3 =70.35–99.33 RU/ml, *n*=220	Quartile 4 >99.33 RU/ml, *n*=210	Per Doubling of FGF23
Model 1	Reference	1.25 (0.90 to 1.73)	1.50 (1.08 to 2.08)	2.96 (2.15 to 4.09)	1.61 (1.43 to 1.81)
Model 2	Reference	1.10 (0.79 to 1.53)	1.34 (0.96 to 1.88)	2.19 (1.54 to 3.13)	1.42 (1.24 to 1.63)
Model 3	Reference	1.07 (0.77 to 1.49)	1.27 (0.91 to 1.79)	2.07 (1.44 to 2.97)	1.37 (1.19 to 1.57)
Model 4a	Reference	1.04 (0.75 to 1.45)	1.24 (0.88 to 1.75)	2.02 (1.41 to 2.91)	1.35 (1.17 to 1.55)
Model 4b	Reference	1.04 (0.74 to 1.45)	1.25 (0.89 to 1.75)	1.99 (1.38 to 2.86)	1.34 (1.17 to 1.55)

Model 1: age, race, and sex. Model 2: model 1, smoking status, BMI, diabetes, CHD, CHF, eGFR (cystatin C equation), and urine ACR. Model 3: model 2, albumin, CRP, and IL-6. Model 4a: model 3, calcium, phosphorus, 25(OH)D, iPTH, and $24,25(OH)_2D$. Model 4b: model 3, calcium, phosphorus, iPTH, and the VMR [$24,25(OH)_2D$-to-25(OH)D ratio]. RU, relative unit.

9th Revision, Clinical Modification (ICD-9-CM) codes were used to ascertain the outcome of interest.

However, there are also several important strengths, including a large number of participants from a community-based population, long-term follow-up, and a large number of infectious hospitalizations. Because of the nature and data collected in the CHS, it was possible to perform comprehensive adjustment for covariates. A large subgroup was also available to study the role of CKD in the association of FGF23 with infectious outcomes. Last, markers of mineral metabolism were measured in a subgroup of participants to provide additional mechanistic insight.

In conclusion, in community-dwelling older adults, higher plasma FGF23 concentrations were independently associated with risk of first infection-related hospitalization. Future studies are needed to confirm postulated mechanisms underlying the associations and determine whether administering $1,25(OH)_2D$ or reducing FGF23 may reduce the risk of infectious outcomes.

CONCISE METHODS

Study Design

The study methods of the CHS, a prospective, longitudinal study of older community-dwelling adults, have been described previously.[24] Briefly, participants were recruited from Medicare eligibility lists within four counties: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Eligible participants were 65 years of age or older, were expected to remain in the area for 3 years after recruitment, were not receiving active treatment for cancer, and were able to provide informed consent without a proxy. The original cohort was recruited in 1989–1990 and a second cohort of 687 black participants was recruited in 1992–1993 for a total of 5888 participants. We conducted FGF23 measurements at the 1996–1997 study visit, which we considered the baseline time point for this analysis. This visit was selected as the baseline visit, because it is the first CHS study visit at which urine collections were obtained for ACR measurement. Among 4413 individuals who participated in this visit, 3406 had eGFR measurements and never previously thawed plasma samples available for FGF23 measurement. Of those, we excluded individuals with missing or insufficient blood specimens for FGF23 measurement (n=69) or missing covariate data (n=196), resulting in a final analytic sample of 3141 participants for this analysis. All participants provided written informed consent, and the study was approved by the investigational review boards at the participating centers.

Study Variables

Plasma FGF23 was measured using a commercially available ELISA kit (Immunotopics, San Clemente, CA) that recognizes two epitopes on the C-terminal side of FGF23.[25] Fasting (8 hours) EDTA plasma specimens collected at the 1996–1997 visit, stored at −70°C, and not previously thawed were thawed in 2010 for measurement. Our estimates of intra-assay and interassay coefficients of variation ranged from 7.4% to 10.6%.

The time to first infection-related hospitalization was determined as any hospitalization with a principal discharge diagnosis of bacteremia, septicemia, endocarditis, pulmonary, genitourinary, gastrointestinal, soft tissue, bone, or joint infection through June 30, 2013. All discharge diagnoses were on the basis of the ICD-9-CM codes (Supplemental Material).

Confounders related to FGF23 and infection-related hospitalization were selected *a priori* as potential covariates, and all were measured during the same study visit as FGF23. Race was determined by self-report and for this analysis, categorized as black or nonblack. Smoking was defined as current, former, or never. Diabetes was defined as the use of insulin or oral hypoglycemic agents, fasting glucose level ≥126 mg/dl, or nonfasting glucose level >200 mg/dl. CHF and CHD were determined on the basis of a combination of self-reported disease at baseline or adjudicated events occurring between baseline and the 1996–1997 study visit. BMI was calculated using body weight measured using a calibrated balance beam scale and height measured with a wall-mounted stadiometer. Cystatin C was measured using a BNII Nephelometer (Dade Behring, Deerfield, IL) and chosen as the primary measure of kidney function.[26] eGFR was calculated for cystatin C using an equation derived from a pooling of cohorts that used iothalamate clearance as the criterion standard ($eGFR=76.7\times \text{cystatin C}^{-1.19}$).[27] Urine ACR (milligrams per gram) was determined from random morning urine samples. Urine albumin was measured by rate nephelometry using the Array 360 CE PROTEIN ANALYZER (Beckman Instruments, Fullerton, CA), and urine creatinine was measured on a Kodak Ektachem 700 Analyzer (Eastman Kodak Company, Rochester, NY). Urine ACR was log transformed for analysis.

CRP was measured using an ELISA developed by the CHS central blood laboratory (CHS Blood Laboratory, Colchester, VT), and IL-6 was measured by ultrasensitive ELISA (R&D Systems, Minneapolis, MN).[28] We took a random sample of 881 individuals at the year 9 examination for additional measurements of mineral markers. Individuals were eligible if they were not missing serum creatinine, cystatin C, or urine ACR. Within this random sample, total 25(OH)D [sum of $25(OH)D_2$ and $25(OH)D_3$] and $24,25(OH)_2D$ were measured using immunoaffinity purification and liquid chromatography-tandem mass spectrometry, and iPTH (Beckman-Coulter DxI Automated TwoSite Immunoassay; Beckman-Coulter, Inc., Brea, CA),[21,29] calcium, and phosphorus were measured using a standard clinical chemistry analyzer. VMR was calculated as the $24,25(OH)_2D$-to-25(OH)D ratio as a reflection of vitamin D adequacy.[23] The subgroup was very similar to the entire cohort in terms of demographics and clinical characteristics.

Statistical Analyses

Covariates were summarized by FGF23 quartile and presented as mean (SD) or median (IQR) for continuous variables and n (%) for categorical variables. Incidence rates were examined by quartile of FGF23 and stratified by eGFR. The longitudinal association between FG23 and first infection-related hospitalization was analyzed using Cox proportional hazards. Participants were censored at death or loss for follow-up. All analyses evaluated FGF23 using

the log-transformed continuous variable and quartiles, with the lowest quartile serving as the reference category. The initial model was adjusted for age, race, and sex. Model 2 was further adjusted for smoking status, BMI, diabetes, CHD, CHF, eGFR, and urine ACR. Model 3 was additionally adjusted for CRP, albumin, and IL-6. Because we were interested in understanding the proposed relationship in participants with and without CKD, we also stratified the analyses by two biomarkers of CKD status (eGFR$<$60 and $\geq$60 ml/min per 1.73 m^2 and urine ACR $\leq$30 and $>$30 mg/g)[30] and tested for multiplicative interactions by CKD status. However, irrespective of *P* values, we planned *a priori* to explore these associations in separate strata according to CKD status, because previous epidemiologic studies have reported stronger association between FGF23 and outcomes in subjects with CKD.[3,19] Additional *post hoc* analyses were performed with stratification by the presence of diabetes, CHF, and CHD.

As a secondary analysis, we repeated the above analyses using a negative binomial regression to examine the association of FGF23 with number of infection-related hospitalizations. We also restricted infection type to bacterial infections or infections considered likely to be bacterial in origin (Supplemental Material). All analyses were also repeated in the subgroup analyses adding serum calcium, phosphorus, iPTH, 25(OH)D, and 24,25$(OH)_2$D (model 4a) or VMR (model 4b) to the final model for 881 participants who were randomly selected for these measurements. Two-tailed values of $P<0.05$ were considered statistically significant for all analyses including interaction terms. All statistical analyses were performed with STATA 12.1.

ACKNOWLEDGMENTS

This research was supported by contracts HHSN268201200036C, HSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086 and grant HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by grants AG023629 and R01HL094555 from the National Institute on Aging and grant K01DK103678 from the National Institute of Diabetes and Digestive and Kidney Diseases. J.H.I. was supported by American Heart Association award 0575021N, which supported fibroblast growth factor 23 and the other mineral metabolism measurements in this study.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication.

A full list of principal Cardiovascular Health Study investigators and institutions can be found at CHS-NHLBI.org.

DISCLOSURES

None.

REFERENCES

1. Stubbs J, Liu S, Quarles LD: Role of fibroblast growth factor 23 in phosphate homeostasis and pathogenesis of disordered mineral metabolism in chronic kidney disease. *Semin Dial* 20: 302–308, 2007
2. Saito H, Maeda A, Ohtomo S, Hirata M, Kusano K, Kato S, Ogata E, Segawa H, Miyamoto K, Fukushima N: Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem* 280: 2543–2549, 2005
3. Ix JH, Katz R, Kestenbaum BR, de Boer IH, Chonchol M, Mukamal KJ, Rifkin D, Siscovick DS, Sarnak MJ, Shlipak MG: Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol* 60: 200–207, 2012
4. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, Chonchol M; HOST Investigators: FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol* 22: 1913–1922, 2011
5. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, Hamm L, Gadegbeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M: Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 79: 1370–1378, 2011
6. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S, Lo J, Ojo A, Sondheimer J, Hsu CY, Lash J, Leonard M, Kusek JW, Feldman HI, Wolf M; Chronic Renal Insufficiency Cohort (CRIC) Study Group: Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA* 305: 2432–2439, 2011
7. Curns AT, Holman RC, Sejvar JJ, Owings MF, Schonberger LB: Infectious disease hospitalizations among older adults in the United States from 1990 through 2002. *Arch Intern Med* 165: 2514–2520, 2005
8. Curns AT, Steiner CA, Sejvar JJ, Schonberger LB: Hospital charges attributable to a primary diagnosis of infectious diseases in older adults in the United States, 1998 to 2004. *J Am Geriatr Soc* 56: 969–975, 2008
9. Dalrymple LS, Katz R, Kestenbaum B, de Boer IH, Fried L, Sarnak MJ, Shlipak MG: The risk of infection-related hospitalization with decreased kidney function. *Am J Kidney Dis* 59: 356–363, 2012
10. Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK: Low vitamin D and High fibroblast growth factor 23 serum levels associate with infectious and cardiac deaths in the HEMO Study. *J Am Soc Nephrol* 27: 227–237, 2015
11. Bacchetta J, Salusky IB, Hewison M: Beyond mineral metabolism, is there an interplay between FGF23 and vitamin D in innate immunity? *Pediatr Nephrol* 28: 577–582, 2013
12. Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstädt HJ, Meersch M, Unruh M, Zarbock A: FGF23 signaling impairs neutrophil recruitment and host defense during CKD. *J Clin Invest* 126: 962–974, 2016
13. Naqvi SB, Collins AJ: Infectious complications in chronic kidney disease. *Adv Chronic Kidney Dis* 13: 199–204, 2006
14. Dalrymple LS, Go AS: Epidemiology of acute infections among patients with chronic kidney disease. *Clin J Am Soc Nephrol* 3: 1487–1493, 2008
15. Ginde AA, Mansbach JM, Camargo CA Jr.: Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 169: 384–390, 2009
16. van Etten E, Stoffels K, Gysemans C, Mathieu C, Overbergh L: Regulation of vitamin D homeostasis: Implications for the immune system. *Nutr Rev* 66[Suppl 2]: S125–S134, 2008
17. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW,

Adams JS, Bloom BR, Modlin RL: Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311: 1770–1773, 2006
18. Jeng L, Yamshchikov AV, Judd SE, Blumberg HM, Martin GS, Ziegler TR, Tangpricha V: Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. *J Transl Med* 7: 28, 2009
19. Jovanovich A, Ix JH, Gottdiener J, McFann K, Katz R, Kestenbaum B, de Boer IH, Sarnak M, Shlipak MG, Mukamal KJ, Siscovick D, Chonchol M: Fibroblast growth factor 23, left ventricular mass, and left ventricular hypertrophy in community-dwelling older adults. *Atherosclerosis* 231: 114–119, 2013
20. Liu S, Quarles LD: How fibroblast growth factor 23 works. *J Am Soc Nephrol* 18: 1637–1647, 2007
21. de Boer IH, Sachs MC, Chonchol M, Himmelfarb J, Hoofnagle AN, Ix JH, Kremsdorf RA, Lin YS, Mehrotra R, Robinson-Cohen C, Siscovick DS, Steffes MW, Thummel KE, Tracy RP, Wang Z, Kestenbaum B: Estimated GFR and circulating 24,25-dihydroxyvitamin D3 concentration: A participant-level analysis of 5 cohort studies and clinical trials. *Am J Kidney Dis* 64: 187–197, 2014
22. Bosworth CR, Levin G, Robinson-Cohen C, Hoofnagle AN, Ruzinski J, Young B, Schwartz SM, Himmelfarb J, Kestenbaum B, de Boer IH: The serum 24,25-dihydroxyvitamin D concentration, a marker of vitamin D catabolism, is reduced in chronic kidney disease. *Kidney Int* 82: 693–700, 2012
23. Berg AH, Powe CE, Evans MK, Wenger J, Ortiz G, Zonderman AB, Suntharalingam P, Lucchesi K, Powe NR, Karumanchi SA, Thadhani RI: 24,25-Dihydroxyvitamin d3 and vitamin D status of community-dwelling black and white Americans. *Clin Chem* 61: 877–884, 2015
24. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Russell TP, Weiler PG: The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1: 263–276, 1991
25. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, Yamamoto T, Hampson G, Koshiyama H, Ljunggren O, Oba K, Yang IM, Miyauchi A, Econs MJ, Lavigne J, Jüppner H: Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med* 348: 1656–1663, 2003
26. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C: Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 352: 2049–2060, 2005
27. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51: 395–406, 2008
28. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B: Cardiovascular mortality risk in chronic kidney disease: Comparison of traditional and novel risk factors. *JAMA* 293: 1737–1745, 2005
29. Mathew JS, Sachs MC, Katz R, Patton KK, Heckbert SR, Hoofnagle AN, Alonso A, Chonchol M, Deo R, Ix JH, Siscovick DS, Kestenbaum B, de Boer IH: Fibroblast growth factor-23 and incident atrial fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). *Circulation* 130: 298–307, 2014
30. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members: Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 158: 825–830, 2013

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2016040401/-/DCSupplemental.

Supplemental Material

Fibroblast Growth Factor 23 and the Risk of Infection-Related Hospitalization in Older Adults

Kristen L Nowak, PhD, MPH, Traci M Bartz, MS, Lorien Dalrymple, MD, MPH, Ian H de Boer, MD, Bryan Kestenbaum, MD, Michael G Shlipak, MD, Pranav S Garimella, MD, MPH, Joachim H Ix, MD, MAS, Michel Chonchol, MD

Supplemental Table 1. Associations (hazard ratios; 95% CI) of fibroblast growth factor 23 with first infection-related hospitalization stratified by the presence of diabetes, congestive heart failure (CHF), and coronary heart disease (CHD)

	Quartile 1 <53.34 RU/mL (n=786)	Quartile 2 53.34-70.34 RU/mL (n=785)	Quartile 3 70.35-99.33 RU/mL (n=786)	Quartile 4 >99.33 RU/mL (n=784)	Per Doubling of FGF23
Diabetes (n=570)					
Model 1	Ref	1.57 [1.03, 2.39]	1.63 [1.07, 2.49]	2.42 [1.61, 3.64]	1.35 [1.19, 1.52]
Model 2	Ref	1.44 [0.94, 2.21]	1.44 [0.93, 2.23]	1.88 [1.19, 2.97]	1.21 [1.05, 1.40]
Model 3	Ref	1.41 [0.92, 2.17]	1.38 [0.89, 2.14]	1.79 [1.13, 2.84]	1.19 [1.02, 1.38]
No Diabetes (n=2571)					
Model 1	Ref	1.13 [0.94, 1.35]	1.21 [1.00, 1.45]	1.69 [1.40, 2.05]	1.26 [1.16, 1.36]
Model 2	Ref	1.03 [0.86, 1.24]	1.01 [0.84, 1.22]	1.22 [0.99, 1.50]	1.11 [1.01, 1.21]
Model 3	Ref	1.03 [0.85, 1.23]	0.99 [0.82, 1.19]	1.17 [0.95, 1.44]	1.08 [0.99, 1.18]
CHF (n=280)					
Model 1	Ref	1.02 [0.47, 2.20]	1.20 [0.58, 2.51]	1.42 [0.72, 2.80]	1.28 [1.08, 1.53]
Model 2	Ref	0.89 [0.40, 2.00]	0.90 [0.41, 1.97]	1.05 [0.49, 2.22]	1.20 [0.98, 1.46]
Model 3	Ref	0.99 [0.44, 2.22]	0.93 [0.42, 2.06]	1.04 [0.49, 2.23]	1.14 [0.93, 1.40]
No CHF (n=2861)					
Model 1	Ref	1.19 [1.00, 1.41]	1.25 [1.05, 1.49]	1.78 [1.49, 2.13]	1.27 [1.18, 1.36]
Model 2	Ref	1.10 [0.92, 1.31]	1.08 [0.90, 1.29]	1.36 [1.12, 1.65]	1.14 [1.06, 1.24]
Model 3	Ref	1.09 [0.92, 1.29]	1.05 [0.88, 1.26]	1.31 [1.07, 1.59]	1.12 [1.04, 1.22]

	Quartile 1 <53.34 RU/mL (n=786)	Quartile 2 53.34-70.34 RU/mL (n=785)	Quartile 3 70.35-99.33 RU/mL (n=786)	Quartile 4 >99.33 RU/mL (n=784)	Per Doubling of FGF23
CHD (n=754)					
Model 1	Ref	1.26 [0.88, 1.80]	1.18 [0.83, 1.68]	1.75 [1.25, 2.44]	1.27 [1.13, 1.43]
Model 2	Ref	1.05 [0.73, 1.51]	1.01 [0.71, 1.45]	1.24 [0.85, 1.81]	1.16 [1.01, 1.33]
Model 3	Ref	1.08 [0.75, 1.55]	0.99 [0.69, 1.43]	1.17 [0.80, 1.71]	1.13 [0.98, 1.30]
No CHD (n=2387)					
Model 1	Ref	1.17 [0.97, 1.41]	1.29 [1.06, 1.56]	1.81 [1.48, 2.20]	1.28 [1.18, 1.39]
Model 2	Ref	1.08 [0.89, 1.31]	1.08 [0.89, 1.32]	1.33 [1.07, 1.65]	1.14 [1.04, 1.24]
Model 3	Ref	1.07 [0.89, 1.30]	1.06 [0.87, 1.29]	1.29 [1.04, 1.60]	1.12 [1.02, 1.22]

ICD-9-CM Infection diagnosis codes, restricted

Those highlighted were included in sub-analysis of bacterial infections or infections considered likely to be bacterial in origin

Bacteremia, Candidemia, Viremia and Sepsis

0031 SALMONELLA SEPTICEMIA

0362 MENINGOCOCCEMIA

0380 STREPTOCOCCAL SEPTICEMIA

03810 STAPHYLCOCC SEPTICEMIA NOS

03811 METHICILLIN SUSCEPTIBLE STAPHYLOCOCCUS AUREUS SEPTICEMIA OCT08-

03812 METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS SEPTICEMIA OCT08-

03819 STAPHYLCOCC SEPTICEMIA NEC

0382 PNEUMOCOCCAL SEPTICEMIA

0383 ANAEROBIC SEPTICEMIA

03840 GRAM-NEG SEPTICEMIA NOS

03841 H. INFLUENAE SEPTICEMIA

03842 E COLI SEPTICEMIA

03843 PSEUDOMONAS SEPTICEMIA

03844 SERRATIA SEPTICEMIA

03849 GRAM-NEG SEPTICEMIA NEC

0388 SEPTICEMIA NEC

0389 SEPTICEMIA NOS

04082 TOXIC SHOCK SYNDROME

0545 HERPETIC SEPTICEMIA

1125 DISSEMINATED CANDIADIASIS

78552 SEPTIC SHOCK

7907 BACTEREMIA

7908 VIREMIA

99591 SIRS-INFECT W/O ORG DYSF (SEPSIS)

99592 SIRS-INFECT W ORGAN DYSF (SEVERE SEPSIS)

Cardiovascular

03282 DIPHTHERITIC MYOCARDITIS

03640 MENINGOCOCC CARDITIS NOS

03641 MENINGOCOCC PERICARDITIS

03642 MENINGOCOCC ENDOCARDITIS

03643 MENINGOCOCC MYOCARDITIS

07420 COXSACKIE CARDITIS, UNSPECIFIED

07421 COXSACKIE PERICARDITIS

07422 COXSACKIE ENDOCARDITIS

07423 COXSACKIE MYOCARDITIS

11281 CANDIDAL ENDOCARDITIS

11503 INFECTION BY HISTOPLASMA CAPSULATUM, PERICARDITIS

11504 INFECTION BY HISTOPLASMA CAPSULATUM, ENDOCARDITIS

11593 HISTOPLASMOSIS UNSPECIFIED, PERICARDITIS

11594 HISTOPLASMOSIS UNSPECIFIED, ENDOCARDITIS

1303 MYOCARDITIS DUE TO TOXOPLASMOSIS

3910 ACUTE RHEUMATIC PERICARDITIS

3911 ACUTE RHEUMATIC ENDOCARDITIS

3912 ACUTE RHEUMATIC MYOCARDITIS

3918 OTHER RHEUMATIC HEART DISEASE

3919 ACUTE RHEUMATIC HEART DISEASE, UNSPEC

3920 RHEUMATIC CHOREA WITH HEART INVOLVEMENT

4210 AC/SUBAC BACT ENDOCARD

4211 AC/SUBAC INFECT ENDOCARD

4219 AC/SUBAC ENDOCARDIT NOS

4220 ACUTE MYOCARDITIS IN DIS SPECIFIED ELSEWHERE

42292 SEPTIC MYOCARDITIS

CNS

00321 SALMONELLA MENINGITIS

0360 MENINGOCOCCAL MENINGITIS

0361 MENINGOCOCC ENCEPHALITIS

0470 MENINGITIS DUE TO ENTEROVIRUS: COXSACKIE

0471 MENIGITIS DUE TO ENTEROVIRUS: ECHO VIRUS

0478 MENINGITIS DUE TO ENTEROVIRUS: OTHER SPECIFIED VIRAL MENIGITIS

0479 MENINGITIS DUE TO ENTEROVIRUS: UNSPECIFIED VIRAL MENINGITIS

048 OTHER ENTEROVIRUS DISEASE OF CENTRAL NERVOUS SYSTEM

0490 LYMPHOCYTIC CHORIOMENINGITIS

0491 MENINGITIS DUE TO ADENOVIRUS

0498 OTHER SPECIFIED NON-ARTHROPOD-BORNE VIRAL DISEASES OF CNS

0499 UNSPECIFIED NON-ARTHROPOD-BORNE VIRAL DISEASES OF CNS

0530 HERPES ZOSTER WITH MENINGITIS

05310 HERPES ZOSTER WITH UNSPEC NERVOUS SYSTEM COMPLICATION

05314 HERPES ZOSTER MYELITIS OCT06

0543 HERPETIC MENINGOENCHEPHALITIS

05472 HERPES SIMPLEX MENINGITIS

05474 HERPES SIMPLEX MYELITIS OCT06

0550 POSTMEASLES ENCEPHALITIS

05600 RUBELLA WITH UNSPECIFIED NEUROLOGIC COMPLICATION

05601 ENCEPHALOMYELITIS DUE TO RUBELLA

05609 RUBELLA WITH NEUROLOGIC COMPLICATIONS, OTHER

05821 HUMAN HERPESVIRUS 6 ENCEPHALITIS

05829 OTHER HUMAN HERPESVIRUS ENCEPHALITIS

0621 WESTERN EQUINE ENCEPHALITIS

0622 EASTERN EQUINE ENCEPHALITIS

0623 ST LOUIS ENCEPHALITIS

0625 CALIFORNIA VIRUS ENCEPHALITIS

0628 OTHER SPECIFIED MOSQUITO BORNE VIRAL ENCEPHALITIS

0629 MOSQUITO BORNE VIRAL ENCEPHALITIS, UNSPECIFIED

0638 OTHER-SPECIFIEC TICK-BORNE VIRAL ENCEPHALITIS

0639 TICK-BORNE VIRAL ENCEPHALITIS, UNSPECIFIED

064 VIRAL ENCEPHALITIS TRANSMITTED BY OTHER AND UNSPECIFIED ARTHROPODS

06641 WEST NILE FEVER WITH ENCEPHALITIS

06642 WEST NILE FEVER WITH OTHER NEUROLOGIC MANIFESTATION

0721 MUMPS MENINGITIS

0722 MUMPS ENCEPHALITIS

1142 COCCIDIOIDAL MENINGITIS

11501 INFECTION BY HISTOPLASMA CAPSULATUM, MENINGITIS

11283 CANDIDAL MENINGITIS

11591 HISTOPLASMOSIS UNSPECIFIED, MENINGITIS

1300 MENINGOENCEPHALITIS DUE TO TOXOPLASMOSIS

3200 HEMOPHILUS MENINGITIS

3201 PNEUMOCOCCAL MENINGITIS

3202 STREPTOCOCCAL MENINGITIS

3203 STAPHYLOCOCC MENINGITIS

3207 MENINGITIS IN OTH BACT DIS

32081 ANAEROBIC MENINGITIS

32082 MENINGITIS GRAM-NEG BCT NEC

32089 MENINGITIS OTH SPCF BACT

3209 BACTERIAL MENINGITIS NOS

3210 CRYPTOCOCCAL MENINGITIS

3211 MENNGITIS IN OTHER FUNGAL DISEASES

3212 MENINGITIS DUE TO VIRUSES NEC

3230 ENCEPHALITIS IN VIRAL DIS CLASS ELSEWHERE OCT06

32301 ENCEPHALITIS AND ENCEPHALOMYELITIS IN VIRAL DIS CLASSIFIED ELSEWHERE OCT06

32302 MYELITIS IN VIRAL DIS CLASSIFIED ELSEWHERE OCT06

3231 ENCEPHALITIS, MYELITIS, AND ENCEPHALOMYELITIS IN RICKETTSIAL DIS CLASSIFIED ELSEWHERE

3234 OTHER ENCEPHALITIS DUE TO INFECT CLASS ELSEWHERE OCT06

32341 OTHER ENCEPHALITIS AND ENCEPHALOMYELITIS DUE TO OTHER INFECT CLASSIFIED ELSE OCT06

32342 OTHER MYELITIS DUE TO OTHER INFECT CLASSIFIED ELSE OCT06

3240 INTRACRANIAL ABSCESS

3241 INTRASPINAL ABSCESS

3249 CNS ABSCESS NOS

Gastronintestinal, Hepatobiliary, Peritonitis & Peritoneal Abscess

03283 DIPHTHERITIC PERITONITIS

5670 PERITONITIS IN INFEC DIS

5671 PNEUMOCOCCAL PERITONITIS

5672 SUPPURAT PERITONITIS NEC

56721 PERITONITIS (ACUTE) GEN OCT05-

56722 PERITONEAL ABSCESS OCT05-

56723 SPONTAN BACT PERITONITIS OCT05-

56729 SUPPURAT PERITONITIS NEC OCT05-

56789 PERITONITIS NEC OCT05-

5679 PERITONITIS NOS

0030 SALMONELLA ENTERITIS

0038 SALMONELLA INFECTION NEC

0039 SALMONELLA INFECTION NOS

0040 SHIGELLA DYSENTERIAE

0041 SHIGELLA FLEXNERI

0043 SHIGELLA SONNEI

0048 SHIGELLA INFECTION NEC

0049 SHIGELLOSIS NOS

0050 STAPH FOOD POISONING

0051 BOTULISM

0052 FOOD POIS D/T C. PERFRIN

0053 FOOD POIS: CLOSTRID NEC

0054 FOOD POIS: V. PARAHAEM

00581 FOOD POISN D/T V. VULNIF

00589 BACT FOOD POISONING NEC

0059 FOOD POISONING NOS

0071 GIARDIASIS

0074 CRYPTOSPORIDIOSIS (Effective Oct 97)

0075 CYCLOSPORIASIS (Effective Oct 2000)

00800 INTEST INFEC E COLI NOS

00801 INT INF E COLI ENTRPATH

00802 INT INF E COLI ENTEROTOXIGENIC

00803 INT INF E COLI ENTEROINVASIVE

00804 INT INF E COLI ENTEROHEMORRHAGIC

00809 INT INF E COLI NEC

0081 ARIZONA ENTERITIS

0082 AEROBACTER ENTERITIS

0083 PROTEUS ENTERITIS

00841 STAPHYLOCOCC ENTERITIS

00842 PSEUDOMONAS ENTERITIS

00843 INT INFEC CAMPYLOBACTER

00844 INT INF YRSNIA ENTRCLTCA

00845 INT INF CLSTRDIUM DFCILE

00846 INTES INFEC OTH ANEROBES

00847 INT INF OTH GRM NEG BCTR

00849 BACTERIAL ENTERITIS NEC

0085 BACTERIAL ENTERITIS NOS

00861 ENTERITIS DUE TO ROTAVIRUS

00862 ENTERITIS DUE TO ADENOVIRUS

00863 ENTERITIS DUE TO NORWALK VIRUS

00864 ENTERITIS DUE TO OTHER SMALL ROUNDS VIRUSES

00865 ENTERITIS DUE TO CALICIVIRUS

00866 ENTERITIS DUE TO ASTROVIRUS

00867 ENTERITIS DUE TO ENTEROVIRUS NEC

00869 ENTERITIS DUE TO OTHER VIRAL ENTERITIS

0088 ENTERITIS DUE TO OTHER ORGANISMS, NOT ELSEWHERE CLASSIFIED

0090 INFECTIOUS COLITIS, ENTERITIS, AND GASTROENTERITIS

0091 COLITIS, ENTERITIS, AND GASTROENTERITIS OF PRESUMED INFECTIOUS ORIGIN

0092 INFECTIOUS DIARRHEA

0093 DIARRHEA OF PRESUMED INFECTIOUS ORIGIN

0392 ACTINOMYCOTIC INFECTIONS - ABDOMEN

0700 VIRAL HEPATITIS A WITH HEPATIC COMA

0701 VIRAL HEPATITIS A WITHOUT MENTION OF HEPATIC COMA

07043 HEPATITIS E WITH HEPATIC COMA

07053 HEPATITIS E W/O HEPATIC COMA

0723 MUMPS PANCREATITIS

07271 MUMPS HEPATITIS

11285 CANDIDAL ENTERITIS

1305 HEPATITIS DUE TO TOXOPLASMOSIS

5400 AC APPEND W PERITONITIS

5401 ABSCESS OF APPENDIX

5409 ACUTE APPENDICITIS NOS

541 APPENDICITIS NOS

542 OTHER APPENDICITIS

56201 DVRTCLI SML INT W/O HMRG

56203 DVRTCLI SML INT W HMRHG

56211 DVRTCLI COLON W/O HMRHG

56213 DVRTCLI COLON W HMRHG

566 ANAL & RECTAL ABSCESS

56781 CHOLEPERITONITIS OCT05-

5695 INTESTINAL ABSCESS

5720 ABSCESS OF LIVER

5721 PORTAL PYEMIA

5750 ACUTE CHOLECYSTITIS (W/O MENTION OF CALCULUS)

57510 CHOLECYSTITIS, UNSPECIFIED

Genitourinary

03284 DIPHTHERITIC CYSTITIS

0720 MUMPS ORCHITIS

59010 AC PYELONEPHRITIS NOS

59011 AC PYELONEPHR W MED NECR

5902 RENAL/PERIRENAL ABSCESS

5903 PYELOURETERITIS CYSTICA

59080 PYELONEPHRITIS NOS

59081 PYELONEPHRIT IN OTH DIS

5909 INFECTION OF KIDNEY NOS

5950 ACUTE CYSTITIS

5954 CYSTITIS IN OTH DIS

59589 CYSTITIS NEC

5959 CYSTITIS NOS

5970 URETHRAL ABSCESS

59800 URETHRAL STRICTURE DUE TO UNSPEC INFECTION

59801 URETHRAL INFECTION DUE TO INFECTION CLASSIFIED ELSEWHERE

5990 URIN TRACT INFECTION NOS

6010 ACUTE PROSTATITIS

6012 ABSCESS OF PROSTATE

6013 PROSTATOCYSTITIS

6014 PROSTATITIS IN OTH DIS

6019 PROSTATITIS NOS

6031 INFECTED HYDROCELE

6040 ORCHITIS WITH ABSCESS

60490 ORCHITIS/EPIDIDYMIT NOS

60491 ORCHITIS IN OTH DISEASE

6071 BALANOPOSTHITIS

6072 INFLAM DIS, PENIS NEC

6080 SEMINAL VESICULITIS

6084 MALE GEN INFLAM DIS NEC

6140 AC SALPINGO-OOPHORITIS OCT05-

6142 SALPINGO-OOPHORITIS NOS OCT05-

6143 ACUTE PARAMETRITIS OCT05-

6145 AC PELV PERITONITIS-FEM OCT05-

6150 AC UTERINE INFLAMMATION OCT05-

6159 UTERINE INFLAM DIS NOS OCT05-

6163 BARTHOLIN'S GLND ABSCESS

6164 ABSCESS OF VULVA NEC

Pulmonary

00322 SALMONELLA PNEUMONIA

01100 TUBERCULOSIS OF LUNG, INFILTRATIVE, UNSPECIFIED

01101 TUBERCULOSIS OF LUNG, INFILTRATIVE, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01102 TUBERCULOSIS OF LUNG, INFILTRATIVE, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01103 TUBERCULOSIS OF LUNG, INFILTRATIVE, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01104 TUBERCULOSIS OF LUNG, INFILTRATIVE, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01105 TUBERCULOSIS OF LUNG, INFILTRATIVE, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01106 TUBERCULOSIS OF LUNG, INFILTRATIVE, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01110 TUBERCULOSIS OF LUNG, NODULAR, UNSPECIFIED

01111 TUBERCULOSIS OF LUNG, NODULAR, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01112 TUBERCULOSIS OF LUNG, NODULAR, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01113 TUBERCULOSIS OF LUNG, NODULAR, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01114 TUBERCULOSIS OF LUNG, NODULAR, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01115 TUBERCULOSIS OF LUNG, NODULAR, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01116 TUBERCULOSIS OF LUNG, NODULAR, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01120 TUBERCULOSIS OF LUNG, WITH CAVITATION, UNSPECIFIED

01121 TUBERCULOSIS OF LUNG, WITH CAVITATION, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01122 TUBERCULOSIS OF LUNG, WITH CAVITATION, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01123 TUBERCULOSIS OF LUNG, WITH CAVITATION, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01124 TUBERCULOSIS OF LUNG, WITH CAVITATION, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01125 TUBERCULOSIS OF LUNG, WITH CAVITATION, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01126 TUBERCULOSIS OF LUNG, WITH CAVITATION, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01130 TUBERCULOSIS OF BRONCHUS, UNSPECIFIED

01131 TUBERCULOSIS OF BRONCHUS, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01132 TUBERCULOSIS OF BRONCHUS , BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01133 TUBERCULOSIS OF BRONCHUS, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01134 TUBERCULOSIS OF BRONCHUS, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01135 TUBERCULOSIS OF BRONCHUS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01136 TUBERCULOSIS OF BRONCHUS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01150 TUBERCULOUS BRONCHIECTASIS, UNSPECIFIED

01151 TUBERCULOUS BRONCHIECTASIS, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01152 TUBERCULOUS BRONCHIECTASIS, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01153 TUBERCULOUS BRONCHIECTASIS, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01154 TUBERCULOUS BRONCHIECTASIS, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01155 TUBERCULOUS BRONCHIECTASIS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01156 TUBERCULOUS BRONCHIECTASIS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01160 TUBERCULOUS PNEUMONIA [ANY FORM], UNSPECIFIED

01161 TUBERCULOUS PNEUMONIA [ANY FORM], BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01162 TUBERCULOUS PNEUMONIA [ANY FORM], BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01163 TUBERCULOUS PNEUMONIA [ANY FORM], TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01164 TUBERCULOUS PNEUMONIA [ANY FORM], TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01165 TUBERCULOUS PNEUMONIA [ANY FORM], TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01166 TUBERCULOUS PNEUMONIA [ANY FORM], TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS]

01170 TUBERCULOUS PNEUMOTHORAX, UNSPECIFIED

01171 TUBERCULOUS PNEUMOTHORAX, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01172 TUBERCULOUS PNEUMOTHORAX, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01173 TUBERCULOUS PNEUMOTHORAX, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01174 TUBERCULOUS PNEUMOTHORAX, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01175 TUBERCULOUS PNEUMOTHORAX, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01176 TUBERCULOUS PNEUMOTHORAX, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01180 OTHER SPECIFIED PULMONARY TUBERCULOSIS, UNSPECIFIED

01181 OTHER SPECIFIED PULMONARY TUBERCULOSIS, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01182 OTHER SPECIFIED PULMONARY TUBERCULOSIS, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01183 OTHER SPECIFIED PULMONARY TUBERCULOSIS, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01184 OTHER SPECIFIED PULMONARY TUBERCULOSIS, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01185 OTHER SPECIFIED PULMONARY TUBERCULOSIS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01186 OTHER SPECIFIED PULMONARY TUBERCULOSIS, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

01190 PULMONARY TUBERCULOSIS, UNSPECIFIED, UNSPECIFIED

01191 PULMONARY TUBERCULOSIS, UNSPECIFIED, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION NOT DONE

01192 PULMONARY TUBERCULOSIS, UNSPECIFIED, BACTERIOLOGICAL OR HISTOLOGICAL EXAMINATION UNKNOWN (AT PRESENT)

01193 PULMONARY TUBERCULOSIS, UNSPECIFIED, TUBERCLE BACILLI FOUND (IN SPUTUM) BY MICROSCOPY

01194 PULMONARY TUBERCULOSIS, UNSPECIFIED, TUBERCLE BACILLI NOT FOUND (IN SPUTUM) BY MICROSCOPY, BUT FOUND BY BACTERIAL CULTURE

01195 PULMONARY TUBERCULOSIS, UNSPECIFIED, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL EXAMINATION, BUT TUBERCULOSIS CONFIRMED HISTOLOGICALLY

01196 PULMONARY TUBERCULOSIS, UNSPECIFIED, TUBERCLE BACILLI NOT FOUND BY BACTERIOLOGICAL OR HISTORICAL EXAMINATION BUT TUBERCULOSIS CONFIRMED BY OTHER METHODS

0310 DIS DUE TO OTHER MYCOBACTERIA: PULMONARY

0330 BORDETELLA PERTUSSIS

0338 WHOOPING COUGH NEC

0339 WHOOPING COUGH NOS

0391 PULMONARY ACTINOMYCOSIS

0521 VARICELLA (HEMORRHAGIC) PNEUMONITIS

0551 POSTMEASLES PNEUMONIA

0730 ORNITHOSIS WITH PNEUMONIA

0796 RSV

1124 CANDIDIASIS OF LUNG

1140 PRIMARY COCCIDIOIDOMYCOSIS

1145 PULMONARY COCCIDIODOMYCOSIS, UNSPECIFIED

11505 HISTOSPLASMA CAPSULATUM, PNEUMONIA

11595 HISTOPLASMOSIS UNSPECIFIED, PNEUMONIA

1304 PNEUMONITIS DUE TO TOXOPLASMOSIS

1363 PNEUMOCYSTOSIS

4650 ACUTE URI OF MULTIPLE OR UNSPEC SITE, ACUTE LARYNGOPHARYNGITIS

4658 ACUTE URI OF MULTIPLE OR UNSPEC SITE, OTHER MULTIPLE SITES

4659 ACUTE URI OF MULTIPLE OR UNSPEC SITE, UNSPEC SITE

4660 ACUTE BRONCHITIS

46611 ACUTE BRONCHIOLITIS DUE TO RSV

46619 ACUTE BRONCHIOLITIS DUE TO OTHER INFECTIOUS ORGANISMS

4800 PNEUMONIA DUE TO ADENOVIRUS

4801 PNEUMONIA DUE TO RSV

4802 PNEUMONIA DUE TO PARAINFLUENZA VIRUS

4803 PNEUMONIA DUE TO SARS-ASSOCIATED CORONAVIRUS

4808 PNEUMONIA DUE TO OTHER VIRUSES NEC

4809 VIRAL PNEUMONIA UNSPECIFIED

481 PNEUMOCOCCAL PNEUMONIA

4820 K. PNEUMONIAE PNEUMONIA

4821 PSEUDOMONAL PNEUMONIA

4822 H.INFLUENZAE PNEUMONIA

48230 STREPTOCOCCAL PNEUMN NOS

48231 PNEUMONIA STREPTOCOCCUS A

48232 PNEUMONIA STREPTOCOCCUS B

48239 PNEUMONIA OTH STREP

48240 STAPHYLOCOCCAL PNEU NOS

48241 METHICILLIN SUSCEPTIBLE PNEUMONIA DUE TO STAPHYLOCOCCUS AUREUS OCT08-

48242 METHICILLIN RESISTANT PNEUMONIA DUE TO STAPHYLOCOCCUS AUREUS OCT08-

48249 STAPH PNEUMONIA NEC

48281 PNEUMONIA ANAEROBES

48282 PNEUMONIA E COLI

48283 PNEUMO OTH GRM-NEG BACT

48284 LEGIONNAIRES' DISEASE

48289 PNEUMONIA OTH SPCF BACT

4829 BACTERIAL PNEUMONIA NOS

4830 MYCOPLASMA PNEUMONIAE

4831 CHLAMYDIA PNEUMONIA

4838 PNEUMONIA DUE TO OTHER SPECIFIED ORGANISM

4841 PNEUMONIA IN CYTOMEGALIC INCLUSION DISEASE

4843 PNEUMONIA IN WHOOPING COUGH

4846 PNEUMONIA IN ASPERGILLOSIS

4847 PNEUMONIA IN OTHER SYSTEMIC MYCOSES

4848 PNEUMONIA IN OTHER INF DIS

485 BRONCHOPNEUMONIA ORG NOS

486 PNEUMONIA, ORGANISM NOS

4870 INFLUENZA WITH PNEUMONIA

4871 INFLUENZA WITH OTHER RESPIRATORY MANIFESTATIONS

488 INFLUENZA DUE TO IDENT AVIAN INFLUENZA VIRUS OCT07- OCT09

4880 INFLUENZA DUE TO IDENT AVIAN INFLUENZA VIRUS OCT09-OCT10

48801 INFLUENZA DUE TO AVIAN INFLUENZA VIRUS WITH PNEUMONIA OCT10

48802 INFLUENZA DUE TO AVIAN INFLUENZA VIRUS WITH OTHER RESPIRATORY MANIF OCT10

4881 INFLUENZA DUE TO IDENT NOVEL H1N1 INFLUENZA VIRUS OCT09-OCT10

48811 INFLUENZA DUE TO 2009 H1N1 INFLUENZA VIRUS WITH PNEUMONIA OCT10

48812 INFLUENZA DUE TO 2009 H1N1 INFLUENZA VIRUS WITH OTHER RESPIRATORY MANIF OCT10

48881 INFLUENZA DUE TO NOVEL INFLUENZA A VIRUS WITH PNEUMONIA OCT11-

48882 INFLUENZA DUE TO NOVEL INFLUENZA A VIRUS WITH OTHER RESPIRATORY MANIF OCT11-

490 BRONCHITIS

49122 OBS CHR BRONC W AC BRONC

4941 BRONCHIECTASIS W AC EXAC

5100 EMPYEMA WITH FISTULA

5109 EMPYEMA W/O FISTULA

5111 BACT PLEUR/EFFUS NOT TB

5130 ABSCESS OF LUNG

5131 ABSCESS OF MEDIASTINUM

5192 MEDIASTINITIS

Skin & Soft Tissue

0311 DIS DUE TO OTHER MYCOBACTERIA: CUTANEOUS

03285 CUTANEOUS DIPHTHERIA

0390 CUTANEOUS ACTINOMYCOSIS

0400 GAS GANGRENE

37601 ORBITAL CELLULITIS

6800 CARBUNCLE OF FACE

6801 CARBUNCLE OF NECK

6802 CARBUNCLE OF TRUNK

6803 CARBUNCLE OF ARM

6804 CARBUNCLE OF HAND

6805 CARBUNCLE OF BUTTOCK

6806 CARBUNCLE OF LEG

6807 CARBUNCLE OF FOOT

6808 CARBUNCLE, SITE NEC

6809 CARBUNCLE NOS

68100 CELLULITIS, FINGER NOS

68101 FELON

68110 CELLULITIS, TOE NOS

68111 ONYCHIA OF TOE

6819 CELLULITIS OF DIGIT NOS

6820 CELLULITIS OF FACE

6821 CELLULITIS OF NECK

6822 CELLULITIS OF TRUNK

6823 CELLULITIS OF ARM

6824 CELLULITIS OF HAND

6825 CELLULITIS OF BUTTOCK

6826 CELLULITIS OF LEG

6827 CELLULITIS OF FOOT

6828 CELLULITIS, SITE NEC

6829 CELLULITIS, SITE NOS

684 IMPETIGO

6850 PILONIDAL CYST WITH ABSCESS

6868 LOCAL SKIN INFECTION NEC

6869 LOCAL SKIN INFECTION NOS

72886 NECROTIZING FASCIITIS

9101 ABRASION OR FRICTION BURN HEAD-INFECTED

9103 BLISTER HEAD-INFECTED

9109 SUPERF IN HEAD NEC-INF

9111 ABRASION TRUNK-INFECTED

9113 BLISTER TRUNK-INFECTED

9119 SUPERF INJ TRNK NEC-INF

9121 ABRASION SHLDR/ARM-INFEC

9123 BLISTER SHOULDER/ARM-INF

9129 SUPERF INJ SHLDR NEC-INF

9131 ABRASION FOREARM-INFECT

9133 BLISTER FOREARM-INFECTED

9139 SUPRF INJ FORARM NEC-INF

9141 ABRASION HAND-INFECTED

9143 BLISTER HAND-INFECTED

9149 SUPERF INJ HAND NEC-INF

9151 ABRASION FINGER-INFECTED

9153 BLISTER FINGER-INFECTED

9159 SUPRF INJ FINGER NEC-INF

9161 ABRASION HIP/LEG-INFECT

9163 BLISTER HIP & LEG-INFECT

9169 SUPERF INJ LEG NEC-INFEC

9171 ABRASION FOOT/TOE-INFEC

9173 BLISTER FOOT & TOE-INFEC

9179 SUPERF INJ FOOT NEC-INF

9191 ABRASION NEC-INFECTED

9193 BLISTER NEC-INFECTED

9199 SUPERFIC INJ NEC-INFECT

Bone & Joint

00323 SALMONELLA ARTHRITIS

00324 SALMONELLA OSTEOMYELITIS

03682 MENINGOCOCC ARTHROPATHY

37603 ORBITAL OSTEOMYELITIS

05671 ARTHRITIS DUE TO RUBELLA

71100 PYOGEN ARTHRITIS-UNSPEC

71101 PYOGEN ARTHRITIS-SHLDER

71102 PYOGEN ARTHRITIS-UP/ARM

71103 PYOGEN ARTHRITIS-FOREARM

71104 PYOGEN ARTHRITIS-HAND

71105 PYOGEN ARTHRITIS-PELVIS

71106 PYOGEN ARTHRITIS-L/LEG

71107 PYOGEN ARTHRITIS-ANKLE

71108 PYOGEN ARTHRITIS NEC

71109 PYOGEN ARTHRITIS-MULT

71140 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE-UNSPEC

71141 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -SHLDER

71142 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -UP/ARM

71143 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -FOREARM

71144 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE PYOGEN ARTHRITIS-HAND

71145 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -PELVIS

71146 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -L/LEG

71147 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -ANKLE

71148 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE NEC

71149 ARTHROPATHY ASSOC WITH OTH BACTERIAL DISEASE -MULT

71150 ARTHROPATHY ASSOC WITH OTH VIRAL DIS-UNSPEC

71151 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -SHLDER

71152 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -UP/ARM

71153 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -FOREARM

71154 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -HAND

71155 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -PELVIS

71156 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -L/LEG

71157 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -ANKLE

71158 ARTHROPATHY ASSOC WITH OTH VIRAL DIS NEC

71159 ARTHROPATHY ASSOC WITH OTH VIRAL DIS -MULT

71160 ARTHROPATHY ASSOC WITH MYCOSES-UNSPEC

71161 ARTHROPATHY ASSOC WITH MYCOSES -SHLDER

71162 ARTHROPATHY ASSOC WITH MYCOSES -UP/ARM

71163 ARTHROPATHY ASSOC WITH MYCOSES -FOREARM

71164 ARTHROPATHY ASSOC WITH MYCOSES -HAND

71165 ARTHROPATHY ASSOC WITH MYCOSES -PELVIS

71166 ARTHROPATHY ASSOC WITH MYCOSES -L/LEG

71167 ARTHROPATHY ASSOC WITH MYCOSES -ANKLE

71168 ARTHROPATHY ASSOC WITH MYCOSES NEC

71169 ARTHROPATHY ASSOC WITH MYCOSES -MULT

71180 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS-UNSPEC

71181 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -SHLDER

71182 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -UP/ARM

71183 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -FOREARM

71184 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -HAND

71185 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -PELVIS

71186 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -L/LEG

71187 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -ANKLE

71188 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS NEC

71189 ARTHROPATHY ASSOC WITH OTHER INFECTIOUS AND PARASITIC DIS -MULT

71190 INF ARTHRITIS NOS-UNSPEC

71191 INF ARTHRITIS NOS-SHLDER

71192 INF ARTHRITIS NOS-UP/ARM

71193 INF ARTHRIT NOS-FOREARM

71194 INF ARTHRIT NOS-HAND

71195 INF ARTHRIT NOS-PELVIS

71196 INF ARTHRIT NOS-L/LEG

71197 INF ARTHRIT NOS-ANKLE

71198 INF ARTHRIT NOS-OTH SITE

71199 INF ARTHRITIS NOS-MULT

73000 AC OSTEOMYELITIS-UNSPEC

73001 AC OSTEOMYELITIS-SHLDER

73002 AC OSTEOMYELITIS-UP/ARM

73003 AC OSTEOMYELITIS-FOREARM

73004 AC OSTEOMYELITIS-HAND

73005 AC OSTEOMYELITIS-PELVIS

73006 AC OSTEOMYELITIS-L/LEG

73007 AC OSTEOMYELITIS-ANKLE

73008 AC OSTEOMYELITIS NEC

73009 AC OSTEOMYELITIS-MULT

73020 OSTEOMYELITIS NOS-UNSPEC

73021 OSTEOMYELITIS NOS-SHLDER

73022 OSTEOMYELITIS NOS-UP/ARM

73023 OSTEOMYELIT NOS-FOREARM

73024 OSTEOMYELITIS NOS-HAND

73025 OSTEOMYELITIS NOS-PELVIS

73026 OSTEOMYELITIS NOS-L/LEG

73027 OSTEOMYELITIS NOS-ANKLE

73028 OSTEOMYELIT NOS-OTH SITE

73029 OSTEOMYELITIS NOS-MULT

73080 BONE INFECT NEC-UNSPEC

73081 BONE INFECT NEC-SHLDER

73082 BONE INFECT NEC-UP/ARM

73083 BONE INFECT NEC-FOREARM

73084 BONE INFECT NEC-HAND

73085 BONE INFECT NEC-PELVIS

73086 BONE INFECT NEC-L/LEG

73087 BONE INFECT NEC-ANKLE

73088 BONE INFECT NEC-OTH SITE

73089 BONE INFECT NEC-MULT

73090 BONE INFEC NOS-UNSP SITE

73091 BONE INFECT NOS-SHLDER

73092 BONE INFECT NOS-UP/ARM

73093 BONE INFECT NOS-FOREARM

73094 BONE INFECT NOS-HAND

73095 BONE INFECT NOS-PELVIS

73096 BONE INFECT NOS-L/LEG

73097 BONE INFECT NOS-ANKLE

73098 BONE INFECT NOS-OTH SITE

73099 BONE INFECT NOS-MULT

Dialysis Access & Central Venous Catheters

99662 INFECT INFLAMM VASCULAR DEVICE IMPLANT GRAFT

99931 OTHER AND UNSPECIFIED INFECTION DUE TO CENTRAL VENOUS CATHETER OCT07-OCT11

99668 INFECT INFLAMM DUE TO PERITONEAL DIALYSIS CATHETER

Device, Procedure, or Surgery- Related

53086 INFECTION OF ESOPHAGOSTOMY

53641 GASTROSTOMY INFECTION

56961 COLOSTY/ENTEROST INFECTN

99660 INFECT INFLAMM DEVICE IMPLANT GRAFT NOS

99661 INFECT INFLAMM CARDIAC DEVICE IMPLANT GRAFT

99663 INFECT INFLAMM NERV DEVICE IMPLANT GRAFT

99664 INFECT INFLAMM URINARY CATH

99665 INFECT INFLAMM GU DEVICE IMPLANT GRAFT

99666 INFECT INFLAMM JOINT PROSTH

99667 INFECT INFLAMM OTH ORTHOP DEVICE IMPLANT GRAFT NOS

99669 INFECT INFLAMM OTH DEVICE IMPLANT GRAFT

99731 VENTILATOR ASSOCIATED PNEUMONIA OCT08-

99802 POSTOPERATIVE SHOCK, SEPTIC

99851 INFECTED POSTOP SEROMA

99859 OTHER POSTOP INFECTION

9993 COMPLIC MEDICAL CARE NEC, OTHER INFECTION - OCT07

99934 ACUTE INFECTION FOLLOWING TRANSFUSION, INFUSION, OR INJECTION BLOOD/PROD OCT11

99939 INFECTION FOLLOWING OTHER INFUSION, INJECTION, TRANSFUSION, OR VACCINATION