**Phenotype Definition: Steroid Induced Osteonecrosis (Validation of St. Jude)**

1. **BioVU (112,516)**

**2. Steroid Exposure (7,315)**

Any corticosteroid

No minimum dose

IV, IM or PO (inhaled does not qualify but does not exclude)

≥ 14 days *cumulative*

**3. Exclusions (3,974)**

Alcohol Abuse (ICD9, or Keyword in Prob List, ever)

Sickle Cell (ICD9, or Keyword in Prob List, ever)

Gaucher (ICD9, or Keyword in Prob List, ever)

Legge-Calve-Perthes (ICD9, or Keyword search in notes, problem lists, reports, ever)

HIV + (ICD 9, Lab, or Keyword in Prob List, ever, OR med mention, ever)

Organ Transplant (ICD 9, CPT, Keyword in Prob List, ever)

**4. Potential Case (run twice: 274+300)**

*[Query window from steroid initiation to termination + 1 year]*

**-FOR-**

A) ICD9 733.4x – Aseptic Necrosis of Bone. Manually reviewed. **N=60+6**

*-OR-*

B) Keywords – “osteonecrosis”, “avascular necrosis”, “AVN”, “aseptic necrosis”, “osteochondritis dessicans”

*without negation. Steroid side-effect phrase ignored (472>214)*. **N=214+294**

**4b. Control**

1, 2 & 3

**-AND-**

Not Included Case (5)

**-AND-**

No bisphosphonates

*\*\*Matched (2:1 or 4:1) to 88 cases by age, gender and PheWAS codes\*\**

**5. Case (88)**

*[Manual Review]*

A) **ICD9 N** = 45/60 + 4/6 **= 49**

B) **Keywords** **N** = 35/214 + 4/294 **= 39**

**Further Information:**

**Corticosteroid Medications**: Cortisone (Cortisone and Cortisone Acetate), Hydrocortisone (Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortisone Acetate, Hydrocortisone Cypionate), Prednisone, Prednisolone (Prednisolone and Prednisolone Sodium Phosphate), Methylprednisolone (Methylprednisolone, Methylprednisolone Sodium Succinate, Methylprednisolone Acetate), Triamcinonlone (Triamcinolone, Triamcinolone Acetonide, Triamcinolone Diacetate, Triamcinolone Hexacetonide), Dexamethasone (Dexamethasone, Dexamethasone Acetate, Dexamethasone Sodium Phosphate), Betamethasone (Betamethasone, Betamethasone Sodium Phosphate, Betamethasone Acetate)

\*\*Steroids not sufficient for case definition: Beclomethasone dipropionate (only inhaled); Budesonide (oral preparation used in Crohn’s disease, but low systemic absorption); Ciclesonide (only inhaled); Fludricortisone (primarily minearalocorticoid, usually dosed with glucocorticoid); Flunisolide (only inhaled); Fluticasone (only inhaled in US); Mometasone Furoate (inhaled only)

Steroids must be given IV, IM, or PO. Topical, inhaled, intranasal, or intra-articular injections are not sufficient (but do not exclude a patient from study) (see spreadsheet for list of qualifying phrases).

**Alcohol Abuse (ICD 9 codes):**

291.\* ALCOHOL INDUCED MENTAL DISORDERS

303.\* ALCOHOL DEPENDENCE

305.0 ALCOHOL ABUSE

305.00 ALCOHOL ABUSE-UNSPEC

305.01 ALCOHOL ABUSE-CONTINUOUS

425.5 Alcoholic Cardiomyopathy

571.0 Alcoholic Liver Diseases

571.1 Alcoholic Liver Diseases

V11.3 Personal History of Alcoholism

**Sickle Cell Disease (ICD 9 codes):**282.41 SICKLE-CELL W/O CRISIS

282.42  SICKLE-CELL WITH CRISIS

282.6    SICKLE-CELL DISEASE

282.60 SICKLE-CELL DISEASE NOS

282.63  SICKLE-CELL/HB-C W/O CRI

282.68 OTHR SICKLE-CEL W/O CRIS

282.69 OTHER SICKLE-CELL W/CRIS

282.64 SICKLE-CEL/HB-C W/CRISIS

**Gaucher (ICD 9 codes):**

272.7 LIPIDOSES

330.1 CEREBRAL LIPIDOSES

**Legg-Calve-Perthes (ICD 9 code):**

732.1 JUV OSTEOCHONDROS PELVIS

**HIV (ICD 9 codes – requires presence of 3 or more codes):**

042 HIV DISEASE

043 HIV CAUSING CONDITN NEC

044 OTHER HIV INFECTION

079.53 HIV 2

795.71 NONSPEC SEROL FIND-HIV

V08 ASYMPTOMATIC HIV STATUS

**ORGAN TRANSPLANT (ICD 9 codes):**

V42 ORGAN TRANSPLANT STATUS

V42.0 KIDNEY TRANSPLANT STATUS

V42.1 HEART TRANSPLANT STATUS

V42.6 LUNG TRANSPLANT STATUS

V42.7 LIVER TRANSPLANT STATUS

V42.8 TRANSPLANT STATUS NEC

V42.81 TRANSPL STAT BONE MARROW

V42.82 TRANSPL STAT STEM CELLS

V42.83 TRANSPL STAT PANCREAS

V42.84 TRANSPL STATUS INTESTINE

V42.89 OTHER TRANSPL STATUS

V42.9 TRANSPLANT STATUS NOS

V58.44 AFTERCARE FOLLO ORG TRAN

996.8 COMPL TRANSPLANTED ORGAN

996.80 COMP ORGAN TRANSPLNT NOS

996.81 COMPL KIDNEY TRANSPLANT

996.82 COMPL LIVER TRANSPLANT

996.83 COMPL HEART TRANSPLANT

996.84 COMPL LUNG TRANSPLANT

996.85 COMPL MARROW TRANSPLANT

996.86 COMPL PANCREAS TRANSPLNT

996.87 COMPL BOWEL TRANSPLANT

996.89 COMP OTH ORGAN TRANSPLNT

**ORGAN TRANSPLANT (CPT codes):**

32851 LUNG TRANSPLANT, SINGLE; WITHOUT CARDIOPULMONARY BYPASS

32852 LUNG TRANSPLANT, SINGLE; WITH CARDIOPULMONARY BYPASS

32853 LUNG TRANSPLANT, DOUBLE (BILATERAL SEQUENTIAL OR EN BLOC); WITHOUT

32854 LUNG TRANSPLANT, DOUBLE (BILATERAL SEQUENTIAL OR EN BLOC); WITH

33935 HEART-LUNG TRANSPLANT WITH RECIPIENT CARDIECTOMY-PNEUMONECTOMY

33945 HEART TRANSPLANT, WITH OR WITHOUT RECIPIENT CARDIECTOMY

38240 BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;

~~29868 ARTHROSCOPY, KNEE, SURGICAL; MENISCAL TRANSPLANTATION (INCLUDES~~

00580 ANESTHESIA FOR HEART TRANSPLANT OR HEART/LUNG TRANSPLANT

38241 BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;

38242 BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;

~~0141T PANCREATIC ISLET CELL TRANSPLANTATION THROUGH PORTAL VEIN, PERCUTANEOUS~~

~~0142T PANCREATIC ISLET CELL TRANSPLANTATION THROUGH PORTAL VEIN, OPEN~~

0085T BREATH TEST FOR HEART TRANSPLANT REJECTION

50360 RENAL ALLOTRANSPLANTATION, IMPLANTATION OF GRAFT; WITHOUT RECIPIENT

50365 RENAL ALLOTRANSPLANTATION, IMPLANTATION OF GRAFT; WITH RECIPIENT

50370 REMOVAL OF TRANSPLANTED RENAL ALLOGRAFT

50380 RENAL AUTOTRANSPLANTATION, REIMPLANTATION OF KIDNEY

44135 INTESTINAL ALLOTRANSPLANTATION; FROM CADAVER DONOR

44136 INTESTINAL ALLOTRANSPLANTATION; FROM LIVING DONOR

44137 REMOVAL OF TRANSPLANTED INTESTINAL ALLOGRAFT, COMPLETE

~~50860 URETEROSTOMY, TRANSPLANTATION OF URETER TO SKIN~~

~~57311 CLOSURE OF URETHROVAGINAL FISTULA; WITH BULBOCAVERNOSUS TRANSPLANT~~

~~60512 PARATHYROID AUTOTRANSPLANTATION (LIST SEPARATELY IN ADDITION TO CODE FOR~~

~~65710 KERATOPLASTY (CORNEAL TRANSPLANT); LAMELLAR~~

~~65730 KERATOPLASTY (CORNEAL TRANSPLANT); PENETRATING (EXCEPT IN APHAKIA)~~

~~65750 KERATOPLASTY (CORNEAL TRANSPLANT); PENETRATING (IN APHAKIA)~~

~~65755 KERATOPLASTY (CORNEAL TRANSPLANT); PENETRATING (IN PSEUDOPHAKIA)~~

~~65780 OCULAR SURFACE RECONSTRUCTION; AMNIOTIC MEMBRANE TRANSPLANTATION~~

76776 ULTRASOUND, TRANSPLANTED KIDNEY, REAL TIME AND DUPLEX DOPPLER WITH IMAGE

47135 LIVER ALLOTRANSPLANTATION; ORTHOTOPIC, PARTIAL OR WHOLE, FROM CADAVER OR

47136 LIVER ALLOTRANSPLANTATION; HETEROTOPIC, PARTIAL OR WHOLE, FROM CADAVER

48160 PANCREATECTOMY, TOTAL OR SUBTOTAL, WITH AUTOLOGOUS TRANSPLANTATION OF

48554 TRANSPLANTATION OF PANCREATIC ALLOGRAFT

48556 REMOVAL OF TRANSPLANTED PANCREATIC ALLOGRAFT

~~0014T "MENISCAL TRANSPLANTATION,~~

32851P "LUNG TRANSPLANT, SINGLE;

32852P "LUNG TRANSPLANT, SINGLE;

33635-50 "HEART-LUNG TRANSPLANT W/

33945P "HEART TRANSPLANT, W/WO RE

S2054 "TRANSPLANTATION MULTIVISC

S2060 "LOBAR LUNG TRANSPLANTATIO

S2103 "ADRENAL TISSUE TRANSPLANT

**Keywords**: alcoholic, sickle cell, Gaucher, HIV, AIDS

**Keywords for Legg-Calve-Perthes**: LCPD; Perthes; Idiopathic Avascular Necrosis; Idiopathic Osteonecrosis.

**Organ transplant keywords**: Staus-post transplant; s/p transplant; bone-marrow transplant; marrow transplant; stem cell transplant; BMT; SCT; kidney transplant; renal transplant; liver transplant; heart transplant; lung transplant; bowel transplant; heart-lung transplant

**Labs for HIV**: Exclude if value ≠ “undetectable” or is NULL; flag record if lab value exists and is = “undetectable” or is NULL

HIV3rd

HIV-1

HIVQnt

HIV-1\_RNA\_Ultraquant

HIV-1\_RNA\_(LOG\_10)

**Steroid side effect phrase** (*ignored for purposes of keyword search*)

“Side effects were discussed with the patient include but are not limited to hyperglycemia, cataracts, thinning of bone, weight gain, glaucoma, hypertension, redistribution of fat and osteonecrosis.”

**PheWAS code matching**

Pulled PheWAS codes from before first ICD9 code for ON, or before first keyword mention.

Determined 30 top PheWAS codes for matching, based on being an indication for steroids (SLE, Aplastic anemia, Neutropenia, Purpura, RA, Pituitary dysfunction, Leukemia, Nephrotic syndrome), marker of steroid exposure (Lipid metabolism, osteoporosis, immune dysfunction, obesity, adrenal insufficiency), infectious complications of steroids, or indicator for severity of disease (Renal failure).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| JD\_CODE | JD\_STR | COUNT | TIER | Reason |
| 695.4 | Lupus erythematosus | 29 | 1 | Indication for steroids |
| 288 | Neutropenia and leukopenia | 21 | 1 | Indication for steroids |
| 285.2 | Anemia of chronic disease | 21 | 1 | Marker of disease severity |
| 287 | Purpura and other hemorrhagic conditions | 20 | 1 | Indication for steroids |
| 041 | Bacterial infection in conditions classified elsewhere and of unspecified site | 20 | 1 | Infectious complication |
| 284 | Aplastic anemia and other bone marrow failure syndromes | 19 | 1 | Indication for steroids |
| 714 | Rheumatoid arthritis and other inflammatory polyarthropathies | 18 | 1 | Indication for steroids |
| 112 | Candidiasis | 17 | 1 | Infectious complication |
| 288.1 | Diseases of white blood cells | 15 | 1 | Indication for steroids |
| 710 | Diffuse diseases of connective tissue | 15 | 1 | Indication for steroids |
| 465 | Acute upper respiratory infections of multiple or unspecified sites | 15 | 1 | Infectious complication |
| 038 | Septicemia | 14 | 1 | Infectious complication |
| 593 | Other disorders of kidney and ureter | 13 | 1 | Indication for steroids, marker of disease severity |
| 790.7 | Bacteremia | 13 | 1 | Infectious complication |
| 599.1 | Urinary tract infection | 13 | 1 | Infectious complication |
| 681 | Superficial cellulitis and abscess | 12 | 1 | Infectious complication |
| 253 | Disorders of the pituitary gland and its hypothalamic control | 12 | 1 | Indication for steroids |
| 473 | Chronic sinusitis | 12 | 1 | Infectious complication |
| 272 | Disorders of lipoid metabolism | 12 | 1 | Marker for steroid exposure |
| 204 | Lymphoid leukemia | 12 | 1 | Indication for steroids |
| 733.0 | Osteoporosis | 11 | 1 | Marker for steroid exposure |
| 202 | Other malignant neoplasms of lymphoid and histiocytic tissue | 11 | 1 | Indication for steroids |
| 279 | Disorders involving the immune mechanism | 10 | 1 | Marker for steroid exposure |
| 278.1 | Obesity | 10 | 1 | Marker for steroid exposure |
| 583 | Nephritis and nephropathy, not specified as acute or chronic | 9 | 1 | Marker of disease severity |
| 255.4 | Corticoadrenal insufficiency or adrenal hypofunction | 9 | 1 | Marker for steroid exposure |
| 791.0 | Proteinuria | 9 | 1 | Indication for steroids, marker of disease severity |
| 995.2 | Sepsis and SIRS | 9 | 1 | Infectious complication |
| 581 | Nephrotic syndrome | 8 | 1 | Indication for steroids, marker of disease severity |
| 586 | RENAL FAILURE NOS | 8 | 1 | Marker of disease severity |

Narrowed the PheWAS codes to:

|  |  |
| --- | --- |
| 695.4 | Lupus erythematosus |
| 287 | Purpura and other hemorrhagic conditions |
| 284 | Aplastic anemia and other bone marrow failure syndromes |
| 714 | Rheumatoid arthritis and other inflammatory polyarthropathies |
| 710 | Diffuse diseases of connective tissue |
| 593 | Other disorders of kidney and ureter |
| 253 | Disorders of the pituitary gland and its hypothalamic control |
| 202, 204 | Lymphoid leukemia, Other malignant neoplasms of lymphoid and histiocytic tissue |
| 581 | Nephrotic syndrome |

1/10/2013

Pulled medications that may be relevant to osteonecrosis (see Steroid ON Meds Table below). Also pulled all medications that could indicate HIV/AIDS, with intent to exclude anyone with HIV (see HIV Meds Table below). Reviewed the latter (HIV meds) and found one control with HIV: Will exclude from analysis (RUID #381345).

|  |
| --- |
| **Steroid ON Meds Table** |
| gemfibrozil |
| atorvastatin |
| fluvastatin |
| lovastatin |
| pravastatin |
| rosuvastatin |
| simvastatin |
| 6-mercaptopurine |
| 6 mercaptopurine |
| mercaptopurine |
| 6-TG |
| 6-thioguanine |
| 6 thioguanine |
| thioguanine |
| azathioprine |
| Methotrexate |
| Bevacizumab (Avastin) |
| l-asparaginase |
| oncaspar |
| peg-asparaginase |
| pegaspargase |
| pegaspariginase |
| peg |
| elspar |
| alteplase |
| tpa |
| heparin |
| warfarin |
| coumadin |
| enoxaparin |
| lovenox |
| lmw heparin |
| antithrombin iii |
| carbamazepine |
| oxcarbazepine |
| phenobarbital |
| phenytoin |
| rifabutin |
| rifampin |
| St. John's wort |
| troglitazone |

|  |
| --- |
| **HIV Meds Table** |
| Abacavir (ABC, Ziagen) |
| Didanosine (ddI, Videx) |
| Emtricitabine (FTC, Emtriva) |
| Lamivudine (3TC, Epivir) |
| Stavudine (d4T, Zerit) |
| Zidovudine (ZDV, AZT, Retrovir) |
| Atazanavir (ATV, Reyataz) |
| Darunavir (DRV, Prezista) |
| Fosamprenavir (FPV, Lexiva) |
| Indinavir (IDV, Crixivan) |
| Lopinavir/ritonavir (LPV/r, Kaletra) |
| Nelfinavir (NFV, Viracept) |
| Ritonavir (RTV, Norvir) |
| Saquinavir (SQV, Fortovase, Invirase) |
| Tipranavir (TPV, Aptivus) |
| Delavirdine (DLV, Rescriptor) |
| Efavirenz (EFV, Sustiva) |
| Etravirine (ETV, Intelence) |
| Nevirapine (NVP, Viramune) |
| Rilpivirine (Edurant) |
| Tenofovir (TDF, Viread) |
| Enfuvirtide (T-20, Fuzeon) |
| Maraviroc (Selzentry) |
| Raltegravir (Isentress) |