MINI-SENTINEL SYSTEMATIC EVALUATION OF HEALTH OUTCOME OF INTEREST DEFINITIONS FOR STUDIES USING ADMINISTRATIVE DATA

INFECTIONS DUE TO BLOOD PRODUCTS, TISSUE GRAFTS, OR ORGAN TRANSPLANTS REPORT

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Systematic Evaluation Of Health Outcome Of Interest Definitions For Studies Using Administrative Data

Infections Due to Blood Products, Tissue Grafts, or Organ Transplants Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was identify algorithms used to detect selected health outcomes of interest using administrative data sources and describe the performance characteristics of these algorithms as reported by the studies in which they were used. This report summarizes the process and findings of the infections related to blood products, tissue grafts, or organ transplants algorithm review.

B. SUMMARY OF FINDINGS

Only one study was identified that validated a coding algorithm for infections in recipients of blood products or tissue grafts, which was a study specific to aspergillosis in transplant recipients. Sixteen studies were identified that studied infections, broadly or specifically defined, in these patients. None of them referenced a validated definition for infections related to blood products or tissue grafts.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

We are unable to provide clear recommendations regarding algorithms that would be acceptable for the study of infections related to blood products, tissue grafts, or organ transplants given the lack of validation studies identified for this review. Aspergillosis was the only validated infection outcome in transplant recipients.[6] One code for aspergillosis had a sensitivity of 63% and PPV of 71%, and another code for pneumonia with aspergillosis had sensitivity of 37%, which would likely be considered suboptimal, but a PPV of 88%. Codes without aspergillosis in the description had much lower positive predictive values, and their sensitivity was also much lower unless combined with the other codes. The combination of the codes with aspergillosis in the description might be useful for studying this outcome, though validation statistics for the combination of only these two codes were not provided.

A number of algorithms for identifying any infection or any hospitalization for infection were described, but none referenced a validation study so the performance characteristics are unknown.

Future work should focus on the validity of a broader set of infection diagnoses if infection is to be studied as a general outcome. If specific infection types are of interest, then the validity of these codes for these specific infection types should be determined.

The code for allogeneic blood transfusion was found to have an acceptable sensitivity (83%) and positive predictive value in one single center study.[12] No validation studies of codes for organ transplantation were referenced by the studies reviewed in this report. Many used the United States Renal Data System, which includes registry data on renal transplant recipients but prohibits review of medical records.

Future efforts to identify validation studies might consider expanding the search to identify studies that may have validated infection codes separately from those validating codes for transfusion, tissue graft, or organ transplants. Though the validation statistics for infection may differ in a population that did not receive these procedures, it may be possible to infer something about the performance of the

algorithms in this way. Alternatively, it may be necessary to perform a new validation study of an algorithm for identifying infections related to transfusion, tissue grafts, or organ transplants. In a separate report on sepsis or septicemia related to blood transfusions, validated algorithms for sepsis and transfusions were reported separately since no study specifically validating sepsis in transfusion recipients was identified.

A final consideration is that it may be challenging to determine whether an infection is related to a blood transfusion, tissue graft, or organ transplant. Some blood transfusions and all tissue grafts or organ transplants are received in the context of an operation, and blood transfusions may be used in patients who have experienced trauma. These types of patients are already at increased risk of infection due to the surgery or trauma, so delineating the source of infection can be difficult. A validation study might focus on specific types of infections thought to be commonly related to transfusions, tissue grafts, or organ transplants, or make special efforts in chart review to determine whether the infection appeared related to these exposures. Immunosuppressant medication-related infection is another classification of infection that might be considered distinctly from those infections carried by blood, tissues, and organs in these groups of patients.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that have been used to identify the HOIs using administrative data.

III. BACKGROUND

The Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and identify the performance characteristics of these algorithms as measured in the studies in which they were used. The data sources of interest were limited to those from the United States or Canada to increase their relevance to the Mini-Sentinel data sources, which are all from the United States. The Mini-Sentinel Protocol Core developed a preliminary list of approximately 140 potential health outcomes of interest, based on several criteria. These criteria included: 1) previous validation studies had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies[1], 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for human drug and biological products[2], 3) the Observational Medical Outcomes Partnership (OMOP)[i] had commissioned reports on algorithms used to identify the health outcome using administrative data.[3]

[i] For more information, visit the OMOP website.

From the original list of 140 HOIs, the Protocol Core worked with FDA to select 20 for which reviews of algorithms would be completed. HOIs for which OMOP had already commissioned reports were purposefully excluded in order to avoid duplication of effort.

Infection related to blood products or tissue grafts was one of the 20 HOIs selected for review. This report describes the review process and findings for infection related to blood product or tissue grafts definition algorithms. Because the search process also included terms to identify organ transplant-related infections, the title and content have been modified to reflect that addition.

IV. METHODS

A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed empirically that the majority of relevant articles from one set of OMOP reports (angioedema)[4,5] would be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, Embase searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

University of Iowa investigators compiled the search results from different databases and eliminated duplicate results using a citation manager program. The results were then output into two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

The search strategy and results for infections related to blood products, tissue grafts, or organ transplants are detailed in the Results section. The PubMed search was conducted on June 23, 2010, and the IDIS search on May 10, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by two investigators to determine whether the full-text article should be reviewed. Initially, 30 abstracts were randomly selected for review so that reviewers could discuss the results and resolve common reasons for disagreement prior to proceeding with all the reviews. Exclusion criteria were documented sequentially (i.e., if exclusion criterion 1 was met then the other criteria were not documented). If the reviewers disagreed on whether the full-text should be

reviewed, then it was selected for review. Inter-rater agreement on whether to include or exclude an abstract was calculated using a Cohen's kappa statistic. The goal was to review any administrative database study that used data from the United States or Canada and studied the HOI, as validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies.

2. Abstract Exclusion Criteria

1. Did not study the HOI.
2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.
3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-Text Review Methods

Full-text articles were reviewed independently by two investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Abstract exclusion criteria were also applied to in the full-text reviews. Full-text review exclusion criteria were applied sequentially, since if fewer than 5 validation studies were identified, up to 10 and possibly more of the articles excluded based on the second criterion would need to be incorporated into the final report. If there was disagreement on whether a study should be included, the two reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator would be consulted to make the final decision.

2. Full-Text Exclusion Criteria

1. Poorly described HOI identification algorithm that would be difficult to operationalize.
2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators were surveyed to request information on any published or unpublished studies that validated an algorithm to identify an HOI in administrative data. Studies that would not be excluded by one of the aforementioned criteria were included in the final report.

E. EVIDENCE TABLE CREATION

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic-expert was consulted to review the results of the evidence table and discuss how they compare and contrast to diagnostic methods currently used in clinical practice. This included whether certain diagnostic codes used in clinical practice were missing from the algorithms, and the appropriateness of the validation definitions compared to diagnostic criteria currently used in clinical practice. A summary of this consultation was included in the results.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed and IDIS searches. The PubMed search identified 401 citations, and the IDIS searches identified 2 citations, one of which was also found in PubMed. The total number of abstracts was 402.

Table 1. PubMed Search Strategy and Results

Search	Query	Results
#1	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "blue cross"[All] OR "health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR “international statistical classification"[All] OR “international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR (“claims”[tw] AND “administrative”[tw]) OR (“data”[tw] AND “administrative”[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields] OR (TennCare [tiab]) OR (RAMQ [tiab]) OR (Cigna [tiab]) OR ((british columbia[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]))) OR (CIHI [All Fields]) OR ((manitoba[tiab]) AND ((center for health policy[all fields]) OR (population[tiab]) OR (health insurance[tiab]))) OR ((ontario[tiab]) AND ((population[tiab]) OR (OHIP[tiab]) OR (registered persons database[tiab]) OR (health insurance [tiab]) OR (ICES[All Fields]) OR (Institute for Clinical Evaluative Sciences[All Fields]))) OR ((Alberta[tiab]) AND ((health[tiab])	373522

	OR (data[tiab]) OR (database[tiab]) OR (population[tiab]) OR (Alberta Health and Wellness[All Fields]))) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	
#2	("Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	2603891
#3	Search #1 NOT #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	253019
#4	infection Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	431637
#5	"transfusion"[All Fields] OR "Blood Transfusion"[Mesh] OR "graft"[All Fields] OR "transplant"[All Fields] OR "transplants"[MESH] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	181839
#6	Search #3 AND #4 and #5 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	689
#7	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR “Predictive Value”[tw]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1863979
#8	Search #6 AND #7 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	401

Table 2. IDIS Search Strategy and Results

All Fields:

("transfusion" or "graft" or "transplant") AND ("Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "GPRD" OR "general practice research database" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR ("Denmark" AND "Epidemiology") OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "THIN" OR "The health improvement network" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM")

AND

Disease:

"INFECTION, BACTERIAL NEC 041." or "MYCOSIS NEC 117." or "DISEASE, MYCOBACTERIA NEC 031." or "INFECT, VIRAL/CHLAMYDIA NEC 079." or "ZYGOMYCOSIS 117.7" or "INFECTION, STREPTOCOCCUS NEC 041.0" or "FILARIASIS AND DRACONTIASIS 125." or "INFECTION, PSEUDOMONAS 041.7" or "INFECTION, MYCOPLASMA NEC 041.81" or "CANDIDIASIS NEC 112." or "INFECTION NEC 136." or "INFECTION, STREPTOCOCCUS D 041.04" or "INFECTION, STAPHYLOCOCCUS NEC 041.1" or "INFECTION, STREPTOCOCCUS C 041.03" or "INFECTION, VIRAL, HPV 079.4" or "INFECTION, HELICOBACTER PYLORI 041.86" or "HELMINTHIASES NEC 128." or "OPISTHORCHIASIS 121.0" or "PLAGUE NEC 020." or " RICKETTSIOSIS NEC 083." or "INFECTION, ACTINOMYCOTIC 039." or "INFECTION, POST-OR/TRAUMA 998.5" or "INFECTION, SALMONELLA NEC 003." or "INFECTION, BLASTOMYCOTIC 116." or "INFECTION, HEMOPHILUS 041.5" or "INFECTION, PROTEUS 041.6" or "INFECTION, RESP, UPPER NEC 465." or "INFECTION, VIRAL, ADENO 079.0" or "HELMINTHIASIS, INTESTINE NEC 127." or "GIARDIASIS 007.1" or "GLANDERS 024." or "EHRLICHIOSIS CHAFFEENSIS 082.41" or "ALLESCHERIOSIS 117.6" or "AMEBIASIS NEC 006." or "ANISAKIASIS 127.1" or "ASCARIASIS 127.0" or "DERMATOMYCOSIS NEC 111." or "PITYRIASIS VERSICOLOR 111.0" or "MELIOIDOSIS 025." or "LISTERIOSIS 027.0" or "TRICHINOSIS 124." or "TRICHURIASIS 127.3" or "DERMATOPHYTOSIS, NAIL 110.1" or "FOOD POISON, BACTERIAL NEC 005." or "COCCIDIOSIS 007.2" or "ANCYLOSTOMIASIS/NECATORIASIS 126." or "INFECTION, URINARY TRACT 599.0" or "INFECTION, STREPTOCOCCUS B 041.02" or "INFECTION, STREPTOCOCCUS A 041.01" or "INFECTION, HIV, ASYMPTOMATIC V08." or "INFECTION, INTEST, VIRUS NEC 008.6" or "INFECTION, MENINGOCOCCAL NEC 036." or "HISTOPLASMOSIS 115." or "INFECTION, CLOSTRIDIUM PERFRIN 041.83" or "PASTEURELLOSIS 027.2" or "CRYPTOCOCCOSIS 117.5" or "GASTRITIS AND DUODENITIS 535." or "HEPATITIS, VIRAL A 070.0" or "HEPATITIS, VIRAL C 070.51" or "DIPHYLLOBOTHRIASIS 123.4" or "DISEASE, CYTOMEGALIC INCLU 078.5" or "DISEASE, INTEST, PROTOZOAL 007." or "ECHINOCOCCOSIS 122." or "CRYPTOSPORIDIOSIS 007.4" or "CYCLOSPORIASIS 007.5" or "DERMATOPHYTOSIS NEC 110." or "COMPLICATION, DEVICE/IMPLANT 996." or "BRUCELLOSIS 023." or "BALANTIDIASIS 007.0" or "BLACK PIEDRA 111.3" or "INFECTION, GONOCOCCAL, PHARY 098.6" or "INFECTION, ERYSIPELOTHRIX 027.1" or "INFECT, RESP SYNCYTIAL VIRUS 079.6" or "INFECTION, PNEUMOCOCCUS 041.2" or "INFECTION, INTEST, BACT NEC 008." or "HETEROPHYIASIS 121.6" or "INFECTION, KLEBSIELLA 041.3" or "INFECTION, RHINOVIRUS 079.3" or "INFECTION, TAENIA SOLIUM 123.0" or "INFECTION, TAENIA SAGINATA 123.2" or "INFECTION, SKIN/SQ NEC 686." or "INFECTIOUS MONONUCLEOSIS 075." or "INFLAMMATION, JAW 526.4" or "ORNITHOSIS 073." or "PARATYPHOID FEVER 002.9" or "SCHISTOSOMA, JAPONICUM 120.2" or "SCHISTOSOMIASIS NEC 120." or "SCHISTOSOMA, MANSONI 120.1" or "LOIASIS 125.2" or "MALARIA, OVALE 084.3" or "MALARIA, VIVAX 084.1" or "INFECTION, VIRAL, ECHO 079.1" or "OMPHALITIS, NEWBORN 771.4" or "TRYPANOSOMIASIS, AFRICAN 086.5" or "TYPHOID FEVER 002.0" or "TRENCH FEVER 083.1" or "TINEA BLANCA 111.2" or "TOXOCARIASIS 128.0" or "PNEUMONIA, SYNCYTIAL VIRUS 480.1" or "POLIOMYELITIS, ACUTE NEC 045." or "Q FEVER 083.0" or "STRONGYLOIDIASIS 127.2" or "INFLAMMATION, PELVIC NEC 614." or "INFECTION, HANTAVIRUS 079.81" or "CHOLANGITIS 576.1" or

"ASPERGILLOSIS 117.3" or "ENTEROBIASIS 127.4" or "DISEASE, ARTHROPOD BORNE NEC 088." or "HERPES, GENITAL 054.1" or "HERPES, GINGIVOSTOMATITIS 054.2" or "INFECTION, CESTODE NEC 123." or "INFLUENZA 487." or "LEISHMANIASIS, MUCOCUTANEOUS 085.5" or "SHIGELLOSIS 004." or "STREPTOBACILLARY FEVER 026.1" or "WHOOPING COUGH 033." or "LEPTOSPIROSIS NEC 100." or "PERITONITIS 567." or "TYPHUS, SCRUB 081.2" or "TUBERCULOSIS, PRIMARY INFECT 010." or "TOXOPLASMOSIS 130." or "INFECTION, RETROVIRUS NEC 079.5" or "INFECTION, PERINATAL NEC 771." or "HERPES SIMPLEX NEC 054." or "GANGRENE, GAS 040.0" or "DISORDER, DIGEST, PERINATAL 777." or "CYSTITIS NEC 595." or "CHANCROID 099.0" or "BRONCHITIS NEC 490." or "CONJUNCTIVITIS, NEWBORN 771.6" or "BABESIOSIS 088.82" or "ARTHROPATHY, INFECTION NEC 711." or "BOTULISM 005.1" or "BARTONELLOSIS 088.0" or "CAPILLARIASIS 127.5" or "DISEASE, PHARYNX NEC 478.2" or "DISEASE, RESP SYST NEC 519." or "FAILURE, RESPIRATORY 799.1" or "FASCIOLOPSIASIS 121.4" or "GASTROENTERITIS, SALMONELLA 003.0" or "GLOSSITIS 529.0" or "HEPATITIS, VIRAL B 070.2" or "INFECTION, INTEST, E COLI 008.0" or "INFECTION, INTEST, PROTEUS 008.3" or "INFECTION, INTEST, ROTAVIRUS 008.61" or "INFECTION, INTEST, YERSINIA 008.44" or "INFECTION, KIDNEY NEC 590." or "INFECTION, INTEST, ADENOVIRUS 008.62" or "INFECTION, AMNIOTIC CAVITY 658.4" or "INFECTION, ESCHERICHIA 041.4" or "INFECTION, GONOCOCCAL NEC 098." or "INFECTION, GONOCOCCAL, ANUS 098.7" or "INFECTION, GONOCOCCAL, EYE 098.4" or "INFECTION, GONOCOCCAL, GU 098.0" or "INFECTION, GONOCOCCAL, JOINT 098.5" or "INFECTION, SPIROCHETAL NEC 104." or "INFECTION, STAPH AUREUS 041.11" or "INFECTION, STREPTOCOCCUS G 041.05" or "LEISHMANIASIS, VISCERAL 085.0" or "INSECT BITE, NONVENOMOUS 919.4" or "INFLAMMATION, PROSTATE 601." or "INFLAMMATION, MALE GENITAL 608.4" or "INFLAMMATION, BREAST 611.0" or "INFECTION, VIRAL, COXSACKIE 079.2" or "INFECTION, TREMATODE NEC 121." or "TRICHOMONIASIS, UROGENITAL 131.0" or "TETANUS 037." or "TINEA NIGRA 111.1" or "SPIRILLARY FEVER, RAT BITE 026.0" or "TUBERCULOSIS, RESP SYST NEC 011." or "TULAREMIA 021." or "TRICHOSTRONGYLIASIS 127.6" or "TRYPANOSOMIASIS NEC 086.9" or "WOUND, OPEN, HAND/FINGER 882." or "WOUND, OPEN, LIMB, LOWER 894." or "TUBERCULOSIS, LYMPH NODE 017.2" or "PG COMPL-INFECTION NEC 647." or "PG COMPL-INFECTION, GU 646.6" or "MEDICAL CARE COMPL-INFECTION 999.3" or "MALARIA, FALCIPARUM 084.0" or "MALARIA, QUARTAN 084.2" or "METAGONIMIASIS 121.5" or "OR-SKIN/SQ TISSUE NEC 86." or "LYME DISEASE 088.81" or "OSTEOMYELITIS NEC 730." or "TRYPANOSOMIASIS, AMERICAN 086.2" or "TUBERCULOSIS, ORGAN NEC 017." or "SYN-ACQ IMMUNE DEFICIENCY 042." or "INFECTION, COLITIS/GASTROENT 009.0" or "EXANTHEMA, VIRAL NEC 057." or "ENCEPHALITIS NEC 323." or "CELLULITIS/ABS-FINGER/TOE 681." or "COCCIDIOIDOMYCOSIS NEC 114." or "ABNORMAL URIN CONSTIT NEC 791." or "CYSTICERCOSIS 123.1" or "BRONCHIECTASIS 494." or "BALANOPOSTHITIS 607.1" or " ENDOPHTHALMITIS, PURULENT 360.0" or " HERPES, MENINGOENCEPHALITIS 054.3" or " INFECTION, VIRAL, CNS 046." or "LEPROSY 030." or "INFECTION, PUERPERAL, MAJOR 670." or "SPOROTRICHOSIS 117.1" or "SYPHILIS NEC 097." or "WHIPPLE`S DISEASE 040.2" or "URETHRITIS, NONSEX TRANSMIT 597." or "VINCENT`S ANGINA 101." or "OTITIS MEDIA, SUPPURATIVE 382." or "PARAGONIMIASIS 121.2" or "LEUKEMIA NEC 208." or "NASOPHARYNGITIS, ACUTE 460." or "PNEUMONIA NEC 483." or "PNEUMONIA, BACTERIAL NEC 482." or "WART, VIRAL 078.1" or "SYNDROME, HEMOPHAGOCYTIC 288.4" or "SINUSITIS, CHRONIC 473." or "KERATITIS NEC 370." or "INFECTION, DIARRHEA 009.2" or "HEPATITIS, VIRAL NEC 070." or "HEMORRHAGIC FEVER NEC 078.6" or "EMPYEMA 510." or "DISEASE, RESP TRACT, UP NEC 478." or "DISEASE, WHITE BLD CELL NEC 288." or "DISEASE, LUNG NEC 518." or "CELLULITIS/ABS-SKIN/SQ NEC 682." or "038.4"

NOT

Descriptor:

("CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168")

NOT

Author:

"(editorial)" or "(Letter to Ed)"

AND

Years:

1990 to 2010

Records = 2

B. ABSTRACT REVIEWS

Of the 402 abstracts reviewed, 183 were selected for full-text review; 97 were excluded because they did not study the HOI, 111 were excluded because they were not administrative database studies, and 10 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of abstracts was 0.32. The major source of disagreement was whether or not a study was an administrative database study. This related to the decision to review single center studies that may have used coding algorithms, and the difficulty in discerning the likelihood of a coding algorithm when reviewing abstracts of such studies.

C. FULL-TEXT REVIEWS

Of the 183 full-text articles reviewed, 1 was included in the final evidence table of validation studies; 15 were excluded because they did not study the HOI, 143 were excluded because they did not use an administrative database, 8 were excluded because the HOI identification algorithm was poorly defined, and 16 were initially excluded but ultimately included in the reported non-validated algorithms because they included no validation of the outcome definition or reporting of validity statistics. Reviewers identified 2 citations for review from full-text article references, both of which were excluded because the algorithms were poorly defined. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 0.66. The one article on which they disagreed included a validation component for hepatitis C diagnosis, but excluded people with organ transplantation and did not focus on blood products as an exposure. Thus, it was ultimately excluded.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators sent no validation studies related to this HOI.

E. EVIDENCE INCLUDED IN TABLE

All of the 17 studies included in the evidence tables were identified from the initial search strategy. None were identified through references of articles that underwent full-text review or by Mini-Sentinel Investigators.

Because fewer than 5 validation studies were identified, 16 studies that did not include validation of the outcome or reporting of validity statistics were reviewed in the evidence table on non-validated definitions.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Only one validation study was identified that examined a definition of infection in recipients of a blood product, tissue graft, or organ transplant (Table 3). Chang et al.[6] studied aspergillosis infections among solid organ or hematopoietic stem cell transplant recipients at a large academic medical center from April 2001 to September 2005. This hospital had a registry developed from an active, prospective surveillance system that was used as a gold standard, and the medical records of registry cases were reviewed to confirm that they met criteria for aspergillosis. ICD-9 billing codes for aspergillosis identified 67 patients, and 38 patients identified by these codes or the registry ultimately had a confirmed case of probable or suspected aspergillosis. Validity statistics were calculated for a variety of ICD-9 codes and combinations of codes. ICD-9 code 117.3 (aspergillosis) appeared to have the best balance between

sensitivity (63%) and positive predictive value (PPV) (71%). ICD-9 code 484.6 (pneumonia with aspergillosis) had a good PPV (88%) but had limited sensitivity (37%), which would be expected since it only describes one type of aspergillosis infection. Though the validity of several combinations of codes was examined, all of these combinations included codes less specific to aspergillosis. This resulted in low PPVs for these combinations, despite good sensitivity. The combination of codes 117.3 and 484.6 might have been expected to achieve a good balance between sensitivity and PPV, but the validation statistics for that combination were not reported. Since this study only included patients from one center, generalizability is limited. In addition, the study methods assumed that the registry had complete ascertainment of aspergillosis cases. This may be a reasonable assumption given the focus on transplant patients and prospective surveillance. ICD-9 codes were also integrated into the active surveillance system after January 2004, so case ascertainment in those patients with billing codes would be expected to be complete after that time. Regardless, no chart review was described for patients identified by billing data who were not in the registry. This is a limitation compared to many studies that perform chart review on all patients identified by billing codes. If the registry did not identify all aspergillosis cases, this would result in increased PPVs and decreased sensitivity for at least some codes.

The 16 studies reviewed that provided algorithms but no validation of the HOI covered a broad range of infections (Table 4). Four studies examined any infections or infection-related hospitalizations.[7-10] The remainder studied more specific types of infection (Table 4). Two studies provided a set of codes to identify coronary artery bypass grafts and transfusions,[8,9] and one provided a set of codes to identify solid organ transplant recipients.[11] The transfusion algorithm which was provided was validated in an earlier study, which found a sensitivity of 83% and specificity of 100% for ICD-9 procedure code 99.04 (allogeneic blood transfusion).[12] Another multi-center study, however, found poor sensitivity (21-31%) despite excellent specificity (100%).[31] Many studies utilized the United States Renal Data System (USRDS), which specifically prohibits chart review by investigators.[13]

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

The only validation study identified included all patients who received a solid organ or hematopoietic stem cell transplant at a single university hospital. The mean age was approximately 51 years (range 16-74) and 68% were male. About half received solid organ transplants and half hematopoietic stem cell transplants.

H. EVIDENCE TABLES

Table 3. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
[6]Chang, et al. 2008	All patients who received solid organ or hematopoietic stem cell transplants (HSCT) at a large academic medical center between April, 2001, and September, 2005, were included in a cohort with prospective, active surveillance. N=67 with an ICD-9 code or an aspergillosis infection in the registry were used to calculate validation statistics. Of the 38 with proven or probable invasive aspergillosis, the mean age was approximately 51 years (range 16-74) and 68% were male. About half received solid organ transplants and half HSCT.	Invasive aspergillosis among solid organ transplant and HSCT recipients.	117.3 (aspergillosis), 117.9 (other and unspecified mycoses), 348.8 (other conditions of the brain: cerebral calcification or fungus), 484.6 (pneumonia with aspergillosis), 484.7 (pneumonia in other systemic mycoses), and 495.4 (malt workers' lung alveolitis due to *Aspergillus clavatus*)	Proven or probable invasive aspergillosis as defined by criteria from an international consensus statement.[14] The medical records of each case in the hospital's registry were independently reviewed by a physician epidemiologist to ensure it met criteria. PPV and sensitivity were calculated for individual ICD-9 codes and combinations of codes. No patient had an ICD-9 code of 495.4, and none of seven patients assigned 348.8 had a proven or probable case (PPV for this code for aspergillosis = 0). *Single codes:* 117.3: Sensitivity = 63% (95% CI 38-84%), PPV = 71% (95% CI 44-90%) 117.9: Sensitivity = 32% (95% CI 13-57%), PPV = 15% (95% CI 6-31%) 484.6: Sensitivity = 37% (95% CI 16-62%), PPV = 88% (95% CI 47-100%) 484.7: Sensitivity = 32% (95% CI 13-57%), PPV = 24% (95% CI 9-45%) *Code combinations:* 117.3 or 117.9: Sensitivity 84% (95% CI 60-97%), PPV 30% (95% CI 18-44) 117.3 or 117.9 or 484.6: Sensitivity 84% (95% CI 60-97%), PPV 30% (95% CI 18-44%) 117.3 or 117.9 or 484.7: Sensitivity 84% (95% CI 60-97%), PPV 28% (95% CI 17-41%) 117.3 or 117.9 or 484.6 or 484.7: Sensitivity 84% (95% CI 60-97%), PPV 28% (95% CI 17-41%)

Table 4. Non-Validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
[15]Abbott, et al. 2001	33,479 primary renal transplant patients in the United States Renal Data System (USRDS) between July 1994 and June 1997. The authors did not report exclusion of any age group.	Bacterial endocarditis within 3 years after first renal transplantation	Bacterial endocarditis was determined from the presence of ICD-9 codes 421.x as a primary hospital discharge diagnosis. Fungal endocarditis was excluded. First renal transplantation identified via USRDS registry Prior hospitalization for valvular heart disease was examined as a risk factor (ICD-9 codes 394.x-397.x and 424.0x-424.1x)
[16]Abbott, et al. 2004	28,942 renal transplant patients in the USRDS transplanted between January 1996 and July 2000. The authors did not report exclusion of any age group.	Urinary tract infections after renal transplantation	Urinary tract infection was defined as at least two ICD-9 codes for the following : 590.x (kidney infection, including pyelonephritis both acute and chronic); 595.0 (acute cystitis); 599.0 (urinary tract infection, not otherwise specified)—(Code listed incorrectly in manuscript as 599.x). Cytomegalovirus disease (ICD-9 code 078.x) and sepsis (ICD-9 code 038.x) were examined as confounders.
[7]Chavers, et al. 2007	368,705 incident pediatric and adult dialysis and transplant patients from 1996-2001 in USRDS. The authors did not report exclusion of any age group.	Infection-related hospitalizations in end-stage renal disease and renal transplant recipients within 3 years of initial presentation	*ICD-9-CM codes were obtained from the author, as the appendix mentioned in the manuscript was not otherwise available.* Urinary tract infection: 590.x, 595.0-595.4, 597.0-597.89, 599.0, 601.x, 604.x, 607.1, 614.0-616.1, 616.3, 616.4, 616.8 Infection and inflammatory reaction due to other vascular device implant and graft (for hemodialysis associated infection): 996.62 Infection and inflammatory reaction due to peritoneal dialysis catheter: 996.68 Any infection (in addition to codes above): 001.x-139.x, 254.1, 320.x-326.x, 331.81, 372.0-372.39, 382.0-382.4, 383.0, 386.33, 386.35, 388.60, 390.x-393.x, 421.x, 422.x, 460.x-466.x, 472.x-474.0, 475.x-477.x, 478.22-478.24, 478.29, 480.x-491.x, 494.x, 510.x, 511.x, 513.x-518.6, 522.5, 522.7, 527.3, 528.3, 540.x-542.x, 566.x, 567.x, 569.5, 572.0-572.2, 573.1-573.3, 575.0-575.12, 611.0, 670.x, 680.x-686.x, 706.0, 711.x, 730.3, 730.8, 730.9, 790.7, 790.8, 730.0-730.2, 997.62,

			998.5, 999.3, V01.x-V06.x, V09.x
[17]Dharnidharka, et al. 2007	870 renal transplant patients from 1996-2000, ≤ 18 years of age, in the USRDS with Medicare as the primary payer.	Urinary tract infections after renal transplantation	The following ICD-9 codes on one institutional claim or at least two physician supplier claims: 590.x (kidney infection, including pyelonephritis both acute and chronic); 595.0x (acute cystitis); 599.x (urinary tract infection, not otherwise specified)—appears this should have been 599.0x since 599.x includes other conditions.
[18]Dharnidharka, et al. 2006	28,924 USRDS Medicare primary renal transplant recipients from January 1996 to July 2000. The authors did not report exclusion of any age group.	Bacterial or viral infections after renal transplantation	Primary discharge ICD-9 diagnoses as follows: 079.x (Unspecified viral infections); 078.5 (cytomegalovirus); 052.9 (varicella); 053.9 (herpes zoster); 038.x (septicemia); 481, 482.9, 486.x (pneumonia); 590.xx, 599.0 (acute pyelonephritis); 682.x (cellulitis).
[19]Hurst, et al. 2009	23,622 adult males in USRDS with Medicare primary insurance who received transplants from January 2000 to July 2005, and without a diagnosis of benign prostatic hyperplasia prior to transplant.	Urinary tract infection (other non-infectious outcomes related to the prostate were also studied)	Urinary tract infection was identified by one institutional claim or two or more physician supplier claims with ICD-9 codes of 590, 590.1, 590.2, 590.8, 590.9, 595, 595.89, 595.9
[20]Johnston, et al. 2007	5117 adult patients in USRDS with Medicare primary insurance who initiated dialysis for failure of a first renal transplant from 1995 to 2004	Sepsis	Sepsis was identified by a hospital discharge diagnosis of 038.xx (septicemia), which include the following: 038.0x (streptococcal); 038.1x (staphylococcal); 038.2 (pneumococcal); 038.3 (anaerobic); 038.4x (aerobic Gram Negative); 038.8 (other specified septicemia); 038.9 (unspecified septicemia).
[21]Klote, et al. 2004	15,870 patients in USRDS with Medicare primary insurance who received renal transplants from January 1998	Tuberculosis	Tuberculosis was identified by an ICD-9 code of 01x.x The following were excluded:

	to July 2000. No age ranges were excluded.		647.x (tuberculosis in pregnancy) V011.x (tuberculosis contact) V032.x (vaccine for tuberculosis) V12.01 (personal history of tuberculosis) 137.x (late effect of tuberculosis)
[22]Kutinova, et al. 2006	44,916 patients in USRDS with Medicare primary insurance who received a first renal transplant from 1995 to 2001. The authors did not report exclusion of any age group.	Sepsis and pneumonia before and after renal transplantation	The presence of sepsis or pneumonia was determined by at least one inpatient or two outpatient claims for the following ICD-9-CM codes: 038.x (sepsis); 480.x-487.x (pneumonia).
[23]Menzin, et al. 2009	11,881 high-risk patients with invasive fungal infections and 11,881 matched high risk controls in the 2004 Healthcare Cost and Utilization Project Nationwide Inpatient Sample. High risk conditions included cancer; infection with human immunodeficiency virus; chronic obstructive pulmonary disease; diabetes mellitus; and solid-organ, hematopoietic stem cell, or bone marrow transplant. All ages were included.	Invasive fungal infection	invasive fungal infection was defined as any primary or secondary diagnosis of one of the following ICD-9-CM codes: 117.3 (aspergillosis); 116.x (blastomycosis); 112.4, 112.5, 112.81, 112.83, 112.85 (candidiasis); 114.0, 114.2, 114.3 (coccidioidomycosis); 117.5 (cryptococcosis); 115.01-115.05, 115.11-115.15, 115.91-115.95 (histoplasmosis); 117.6, 117.9 (other mycoses); 117.7 (zygomycosis).
[13]Neff, et al. 2009	32,757 patients in USRDS with Medicare primary insurance who received renal transplants from January 2000 to July 2004. The authors did not report exclusion of any age group.	*Pneumocystis jiroveci* pneumonia (PCP) Cytomegalovirus (CMV) was examined as a risk factor	The following ICD-9 CM codes were used in this study: 136.3 (PCP); 078.5 (CMV).
[9]Rogers, et al. 2009	24.789 fee-for-service Michigan Medicare beneficiaries $\geq$ 65 years of age who received coronary artery bypass graft (CABG) surgery from 2003 to 2006.	Infection during hospitalization CABG and transfusion codes were also provided	CABG surgery was identified by ICD-9 procedure codes 36.1x Blood transfusions were identified from procedure codes (99.0x) in addition to revenue codes for blood products and services (38x for purchased blood and 39x for donated blood). Allogeneic transfusions could include red blood cells, whole blood, platelets, plasma, or cyroprecipitates. Autologous blood transfusions were identified using procedure codes 99.00 (perioperative autologous transfusion of

			whole blood or blood components) or 99.02 (transfusion of previously collected autologous blood). The code for allogeneic red blood cell transfusion (99.04) was previously found to have a sensitivity of 83% and specificity of 100% in a single-center study.[12] Infection codes were not fully described. "We determined infection by using ICD-9 codes that explicitly stated infection (for example, 0xx.xx) or provided evidence of infection (purulent, suppurative, septic, pyogenic or abscess)"
[8]Rogers, et al. 2006	9218 Michigan Medicare beneficiaries ≥ 65 years of age with CABG surgery from July 1997 to Sept 22nd 1998.	Infection during hospitalization CABG and transfusion codes were also provided	CABG surgery was identified by ICD-9 procedure codes 36.1x Blood transfusions were identified by the above listed codes used in Rogers, et al., 2009, which were found to have a sensitivity of 83% and specificity of 100%.[12] *The following ICD-9 primary and secondary codes from hospitalization data were used to identify infections:* Infectious and parasitic diseases (001-136); Infections indicated in the nervous system and sense organs (380.1, 382); Infections of the circulatory system (420-422, 440.24); Infections of the respiratory system (460-466, 473, 478.29, 480-487, 491.1, 511.1, 513.0, 513.1, 519.2); Infections of the digestive system (528.2, 540, 550.0, 567.0-567.2, 595.5, 569.61, 575.0, 577.0); Infections of the genitourinary system (590, 595.0, 599.0, 604.9, 616.1,); Infections of the skin and subcutaneous tissue (680-686); Infections of the musculoskeletal system (711.0, 711.3-711.9, 728.0, 730.0); Bacteremia (790.7); Infection and inflammatory reaction due to internal prosthetic implant and graft (996.6); Post-operative infection not elsewhere classified (998.50);

			Other infection due to medical care not elsewhere classified (999.3); and V-codes (V08—asymptomatic infection with HIV, V09—Infection with drug-resistant microorganisms).
[24]Shroff, et al. 2008	47,899 first time renal transplant recipients and 62,520 renal transplant waiting list patients with Medicare primary insurance in USRDS from 1995-2003. The authors did not report exclusion of any age group.	Hospitalization for bacterial endocarditis	Bacterial endocarditis was identified by ICD-9-CM code 421.0 Infectious organisms were identified by ICD-9-CM codes 038.xx and 041.xx during the same hospitalization as the bacterial endocarditis claim
[10]Snyder, et al. 2009	46,471 adult (≥ 18 years of age) first renal transplant patients in the USRDS from 1995-2003 with Medicare primary insurance coverage. Patients under 62 years of age were followed for up to 3 years since this is the duration of automatic Medicare coverage post-transplant. Patients 62 years and older were followed for up to 5 years since they would be Medicare eligible when the 3 year term expired.	First infection following renal transplantation. The algorithm only includes infections that can be attributed to specific categories of pathogens. Hospitalizations due to urinary tract infections, pneumonia, and other infections that could not be attributed to specific causal agents were included in the study, but ICD-9-CM codes were not provided for these types of infections.	*ICD-9-CM codes by infection type:* *Bacterial:* Septicemia: 038.x Tuberculosis: 010.x-018.x Other bacterial: 001.x-004.x, 008.0x-008.5x, 020.x-027.x, 030.x-036.x, 039.x-041.x, 073.x, 076.x, 080.x-083.x, 087.x-088.x, 091.x-100.x, 102.x-104.x, 137.x *Viral:* Hepatitis B: 070.2x, 070.3x Hepatitis C: 070.41, 070.44, 070.51, 070.54 Hepatitis (other): 070.0x-070.1x, 070.42, 070.43, 070.49, 070.52, 070.53, 070.59, 070.6x, 070.9x Cytomegalovirus: 078.5x Other viral: 008.6x, 008.8x, 045.x-051.x, 055.x-057.x, 060.x-066.x, 071.x, 072.x, 074.x, 075.x, 078.2x-078.4x, 078.6x, 078.7x, 079.51, 079.52, 079.81 *Fungal:* 112.0x, 112.4x, 112.5x, 112.81, 112.83, 112.84, 112.85, 112.89, 112.9x, 114.x-117.x *Parasitic:* Pneumocystosis: 136.3x Other parasitic: 006.x, 007.x, 084.x-086.x, 120.x-131.x, 136.2x, 136.4x, 136.5x *Other:* 009.x, 101.x, 136.9x *Note:* Despite no validation of the HOI, the sensitivity of 3 algorithms for identifying infections was compared in a secondary analysis. The primary analysis required one inpatient or two outpatient

			claims for an infection to consider one present. If only inpatient claims were considered, the overall infection rates were 44% lower than in the primary analysis. Hospitalization data-only identified 35, 51, 44, and 70% of bacterial, viral, fungal, and parasitic infections identified in the primary analysis. When the criterion of two outpatient claims was loosened to require only one outpatient claim, the overall infection rate was increased by 10%. The rates of bacterial, viral, fungal, and parasitic infections increased by 19, 25, 9, and 37%, respectively, compared to the primary analysis.
[11]Tong, et al. 2009	The analysis included everyone in the 2003 Nationwide Inpatient Sample, part of the Healthcare Cost and Utilization Project, which represents approximately 7.5 million hospital stays in a stratified sample of 20% of all US community hospitals. It also included 100% of Medicare Beneficiary hospitalizations for 2003 from the Medicare Provider Analysis and Review file, approximately 11.5 million records. All ages were included.	Invasive aspergillosis Solid organ tranplantation codes were also described	Aspergillosis was identified by a primary or secondary hospital discharge diagnosis ICD-9 code of 117.3. Pneumonia in aspergillosis was identified by ICD-9 code 117.3 with ICD-9 code 484.6 as a secondary diagnosis. Solid organ transplantation hospitalizations were identified by DRGs 103, 302, 480, and 495 ICD-9-CM codes for complications of transplants were used to identify post-transplant hospitalizations, since a DRG is not available to describe post-transplant status. These included: complications of transplanted kidney (996.81), liver (996.82), heart (996.83), lung (996.84), and bone marrow (996.85).

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Algorithms for detection of the health outcome of interest, infections related to blood products, tissue grafts, or organ transplant, using administrative data are currently of limited value. There are no known published validation studies that have looked at administrative data and infections associated with receipt of blood products or tissue grafts. Validation studies could be performed to examine the agreement of infection diagnoses in administrative data and clinical data, but the challenge of linking the infection to the transfusion or graft would still remain.

The only study that validated in an infection outcome was one that looked at aspergillosis in hematopoietic stem cell transplants and solid organ transplants. The sensitivity of ICD-9 code 117.3 was described as modest (63%) and the code 117.9 was described as poor (32%). If either code was present, the sensitivity was 84%, but the positive predictive value was 30%, which would likely be considered unacceptable. Even this study was limited by the fact that it was a single center study and it was unlikely that these infections were transmitted by the transplanted tissue or cells. These infections would have been secondary to the necessary immune suppression that these transplant recipients must receive. The other non-validated studies had similar limitations in that they detected infections due to immune

suppression and not receipt of the graft of interest. Thus, it is unlikely that the codes/algorithm detect a problem associated with medical product of interest.

One general concern of the administrative data approach is that infections that used to be more commonly, though still rarely, transmitted with these blood products or tissue grafts are now screened for at donation. Thus, the likelihood of transmission of viral hepatitis or HIV from these sources is very rare and declining.[25-28] In addition, the time from transplant to infection recognition is long and thus it would be difficult to link the two. Currently, infections linked to receipt of blood products or tissue grafts are often of microbiologically very rare organisms. Several example being the recent report of transplant-associated encephalitis from the donor to the two kidney recipients of Balamuthia granulomatous amebic encephalitis (GAE), a rare disease caused by Balamuthia mandrillaris, a free-living ameba found in soil.[29] This was identified by physician self-report to the CDC. Recent cases of rabies transmission via solid organ transplantation are another example of an extremely rare event that would not be detected via administrative data, but by other reporting mechanisms.[30] Recent efforts at mandatory reporting have identified many of these cases for investigation by public health experts, but this can only occur after astute recognition by involved clinicians.

Though no data support this assertion, it seems likely that surveillance of transfusion, graft, or transplant associated infections would be limited by the lack of sensitivity of both clinical and administrative data. Even if the administrative data were highly sensitive to clinically diagnosed infections, linking them to the transfusion or graft can pose challenges in the clinical setting, and even greater challenges in administrative data.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

We are unable to provide clear recommendations regarding algorithms that would be acceptable for the study of infections related to blood products or tissue grafts given the lack of validation studies identified for this review. Aspergillosis was the only validated infection outcome in transplant recipients.[6] One code for aspergillosis had a sensitivity of 63% and PPV of 71%, and another code for pneumonia with aspergillosis had sensitivity of 37%, which would likely be considered suboptimal, but a PPV of 88%. Codes without aspergillosis in the description had much lower positive predictive values, and their sensitivity was also much lower unless combined with the other codes. The combination of the codes with aspergillosis in the description might be useful for studying this outcome, though validation statistics for the combination of only these two codes were not provided.

A number of algorithms for identifying any infection or any hospitalization for infection were described, but none referenced a validation study so the performance characteristics are unknown.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Future work should focus on the validity of a broader set of infection diagnoses if infection is to be studied as a general outcome. If specific infection types are of interest, then the validity of these codes for these specific infection types should be determined.

The code for allogeneic blood transfusion was found to have an acceptable sensitivity (83%) and positive predictive value in one single center study,[12] but poor sensitivity (21-31%) despite excellent specificity in

another multi-center study from the late 1980s.[31] No validation studies of codes for tissue grafts or organ transplantation were referenced by the studies reviewed in this report. Many used USRDS data, which includes registry data on renal transplant recipients.

Future efforts to identify validation studies might consider expanding the search to identify studies that may have validated infection and transfusion or tissue graft codes separately. Though the validation statistics for infection may differ in a population that did not receive these procedures, it may be possible to infer something about the performance of the algorithms in this way. Alternatively, it may be necessary to perform a new validation study of an algorithm for identifying infections related to transfusion or tissue grafts. In a separate report on sepsis or septicemia related to blood transfusions, validated algorithms for sepsis and transfusions were reported separately since no study specifically validating sepsis in transfusion recipients was identified.

A final consideration is that it may be challenging to determine whether an infection is related to a blood transfusion, tissue graft, or organ transplant. Some blood transfusions and all tissue grafts and organs are received in the context of an operation, and blood transfusions may be used in patients who have experienced trauma. These types of patients are already at increased risk of infection due to the surgery or trauma, so delineating the source of infection can be difficult. A validation study might focus on specific types of infections thought to be commonly related to transfusions, tissue grafts, or organs, or make special efforts in chart review to determine whether the infection appeared related to these exposures. Immunosuppressant medication-related infection is another classification of infection that might be considered distinctly from those infections carried by blood, tissues, or organs in these groups of patients.

VII. REFERENCES

1. West SL, Strom BL, Poole C. Validity of pharmacoepidemiologic drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. Chichester: John Wiley, 2005. 709-766.

2. FDA Designated Medical Events (DME). Listing of DMEs is adapted from "Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule" at http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf. Accessed 6/4/2010.

3. The Observational Medical Outcomes Partnership (OMOP). Health Outcomes of Interest. Available at: http://omop.fnih.org/HOI. Accessed 6/4/2010.

4. Jarrett N, Lux L, West S. Systematic evaluation of health outcome of interest definitions in observational studies and clinical definitions for the Observational Medical Outcomes Partnership: angioedema: report. Available at: http://omop.fnih.org/sites/default/files/RTI%20Angioedema%20Final%20Report%20110509.pdf Accessed 6/7/10.

5. Kachroo S, Jones N, Reynolds MW. Systematic literature review for evaluation of angioedema. Final report prepared for the Foundation of the National Institutes of Health via the Observational Medical Outcomes Partnership. Available at: http://omop.fnih.org/sites/default/files/UBC-OMOP%20Systematic%20Lit%20Review%20Angioedema%20Final%20Report%209-11-2009.pdf. Accessed 6/7/10.

6. Chang DC, Burwell LA, Lyon GM, et al. Comparison of the use of administrative data and an active system for surveillance of invasive aspergillosis. *Infect Control Hosp Epidemiol*. 2008; 29: 25-30.

7. Chavers BM, Solid CA, Gilbertson DT, Collins AJ. Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. *J Am Soc Nephrol*. 2007; 18: 952-959.

8. Rogers MA, Blumberg N, Saint SK, Kim C, Nallamothu BK, Langa KM. Allogeneic blood transfusions explain increased mortality in women after coronary artery bypass graft surgery. *Am Heart J*. 2006; 152: 1028-1034.

9. Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: A cohort study. *BMC Med*. 2009; 7: 37.

10. Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. *Kidney Int*. 2009; 75: 317-326.

11. Tong KB, Lau CJ, Murtagh K, Layton AJ, Seifeldin R. The economic impact of aspergillosis: Analysis of hospital expenditures across patient subgroups. *Int J Infect Dis*. 2009; 13: 24-36.

12. Segal JB, Ness PM, Powe NR. Validating billing data for RBC transfusions: a brief report. *Transfusion*. 2001; 41(4): 530-533.

13. Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: Incidence and risk factors for pneumocystis jiroveci pneumonia. *Transplantation*. 2009; 88: 135-141.

14. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*. 2002; 34: 7-14.

15. Abbott KC, Duran M, Hypolite I, Ko CW, Jones CA, Agodoa LY. Hospitalizations for bacterial endocarditis after renal transplantation in the United States. *J Nephrol*. 2001; 14: 353-360.

16. Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis*. 2004; 44: 353-362.

17. Dharnidharka VR, Agodoa LY, Abbott KC. Effects of urinary tract infection on outcomes after renal transplantation in children. *Clin J Am Soc Nephrol*. 2007; 2: 100-106.

18. Dharnidharka VR, Caillard S, Agodoa LY, Abbott KC. Infection frequency and profile in different age groups of kidney transplant recipients. *Transplantation*. 2006; 81(12): 1662-7.

19. Hurst FP, Neff RT, Falta EM, et al. Incidence, predictors, and associated outcomes of prostatism after kidney transplantation. *Clin J Am Soc Nephrol*. 2009; 4: 329-336.

20. Johnston O, Zalunardo N, Rose C, Gill JS. Prevention of sepsis during the transition to dialysis may improve the survival of transplant failure patients. *J Am Soc Nephrol*. 2007; 18: 1331-1337.

21. Klote MM, Agodoa LY, Abbott K. Mycobacterium tuberculosis infection incidence in hospitalized renal transplant patients in the United States, 1998-2000. *Am J Transplant*. 2004; 4: 1523-1528.

22. Kutinova A, Woodward RS, Ricci JF, Brennan DC. The incidence and costs of sepsis and pneumonia before and after renal transplantation in the United States. *Am J Transplant*. 2006; 6: 129-139.

23. Menzin J, Meyers JL, Friedman M, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. *Am J Health Syst Pharm*. 2009; 66: 1711-1717.

24. Shroff GR, Skeans M, Herzog CA. Outcomes of renal transplant and waiting list patients with bacterial endocarditis in the United States. *Nephrol Dial Transplant*. 2008; 23: 2381-2385.

25. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious disease risks of blood transfusions. *J Am Med Assoc*. 2003; 289(8): 959-62.

26. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006; 44: S6-S9.

27. Centers for Disease Control and Prevention (CDC). HIV transmission through transfusion—Missouri and Colorado, 2008. *MMWR Morb Mortal Wkly Rep*. 2010; 59(41): 1335-9.

28. Schweitzer EJ, Perencevich EN, Philosophe B, Bartlett ST. Estimated benefits of transplantation of kidneys from donors at increased risk for HIV or hepatitis C infection. *Am J Tranplant*. 2007; 7(6): 1515-25.

29. Centers for Disease Control and Prevention (CDC). Balamuthia mandrillis transmitted through organ transplantation—Mississippi, 2009. *MMWR Morb Mortal Wkly Rep*. 2010; 59(36): 1165-70.

30. Maier T, Schwarting A, Maurer D, et al. Management and outcomes after multiple corneal and solid organ transplantations from a donor infected with rabies virus. *Clinical Infectious Diseases*. 2010; 50: 1112–1119.

31. Romano PS, Mark DH. Bias in coding of hospital discharge data and its implications for quality assessment. *Medical Care*. 1994; 32(1): 81-90.

VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLE

1. Abstract of the Validation Study

Chang DC, Burwell LA, Lyon GM, et al. Comparison of the use of administrative data and an active system for surveillance of invasive aspergillosis. *Infect Control Hosp Epidemiol*. 2008; 29: 25-30.

BACKGROUND: Administrative data, such as International Classification of Diseases, Ninth Revision (ICD-9) codes, are readily available and are an attractive option for surveillance and quality assessment within a single institution or for interinstitutional comparisons. To understand the usefulness of administrative data for the surveillance of invasive aspergillosis, we compared information obtained from a system based on ICD-9 codes with information obtained from an active, prospective surveillance system, which used more extensive case-finding methods (Transplant Associated Infection Surveillance Network). METHODS: Patients with suspected invasive aspergillosis were identified by aspergillosis-related ICD-9 codes assigned to hematopoietic stem cell transplant recipients and solid organ transplant recipients at a single hospital from April 1, 2001, through January 31, 2005. Suspected cases were classified as proven or probable invasive aspergillosis by medical record review using standard definitions. We calculated the sensitivity and positive predictive value (PPV) of identifying invasive aspergillosis by individual ICD-9 codes and by combinations of codes. RESULTS: The sensitivity of code 117.3 was modest (63% [95% confidence interval {CI}, 38%-84%]), as was the PPV (71% [95% CI, 44%-90%]); the sensitivity of code 117.9 was poor (32% [95% CI, 13%-57%]), as was the PPV (15% [95% CI, 6%-31%]). The sensitivity of codes 117.3 and 117.9 combined was 84% (95% CI, 60%-97%); the PPV of the combined codes was 30% (95% CI, 18%-44%). Overall, ICD-9 codes triggered a review of medical records for 64 medical patients, only 16 (25%) of whom had proven or probable invasive aspergillosis. CONCLUSIONS: A surveillance system that involved multiple ICD-9 codes was sufficiently sensitive to identify most cases of invasive aspergillosis; however, the poor PPV of ICD-9 codes means that this approach is not adequate as the sole tool used to classify cases. Screening ICD-9 codes to trigger a medical record review might be a useful method of surveillance for invasive aspergillosis and quality assessment, although more investigation is needed.

2. Abstracts of the Studies with Non-Validated Algorithms

Abbott KC, Duran M, Hypolite I, Ko CW, Jones CA, Agodoa LY. Hospitalizations for bacterial endocarditis after renal transplantation in the United States. *J Nephrol*. 2001; 14: 353-360.

PURPOSE: The national rate of and risk factors for bacterial endocarditis in renal transplant recipients has not been reported. METHODS: Retrospective registry study of 33,479 renal transplant recipients in the United States Renal Data System (USRDS) between 1 July 1994 and 30 June 1997. Hospitalizations for a primary diagnosis of bacterial endocarditis (ICD-9 codes 421.x) within three years after renal transplant were assessed. RESULTS: Renal transplant recipients had an unadjusted incidence ratio for endocarditis of 7.84 (95% confidence interval 4.72-13.25) in 1996. In multivariate analysis, a history of hospitalization for valvular heart disease (adjusted odds ratio (AOR), 25.81, 95% confidence interval 11.28-59.07), graft loss (AOR, 2.81, 95% CI 1.34-5.09), and increased duration of dialysis prior to transplantation were independently associated with hospitalizations for bacterial endocarditis after transplantation. Hospitalization for endocarditis was associated with increased patient mortality in Cox Regression analysis, hazard ratio 4.79, 95% CI 2.97-6.76. CONCLUSIONS: The

overall incidence of bacterial endocarditis was much greater in renal transplant recipients than in the general population, although it is still relatively infrequent. Independent risk factors for bacterial endocarditis in the renal transplant recipients were identified, the most significant of which was valvular heart disease. Endocarditis substantially impacts renal transplant recipient survival.

Abbott KC, Swanson SJ, Richter ER, et al. Late urinary tract infection after renal transplantation in the United States. *Am J Kidney Dis*. 2004; 44: 353-362.

BACKGROUND: Although urinary tract infection (UTI) occurring late after renal transplantation has been considered "benign," this has not been confirmed in a national population of renal transplant recipients. METHODS: We conducted a retrospective cohort study of 28,942 Medicare primary renal transplant recipients in the United States Renal Data System (USRDS) database from January 1, 1996, through July 31, 2000, assessing Medicare claims for UTI occurring later than 6 months after transplantation based on International Classification of Diseases, 9th Revision (ICD-9), codes and using Cox regression to calculate adjusted hazard ratios (AHRs) for time to death and graft loss (censored for death), respectively. RESULTS: The cumulative incidence of UTI during the first 6 months after renal transplantation was 17% (equivalent for both men and women), and at 3 years was 60% for women and 47% for men (P < 0.001 in Cox regression analysis). Late UTI was significantly associated with an increased risk of subsequent death in Cox regression analysis (P < 0.001; AHR, 2.93; 95% confidence interval [CI], 2.22, 3.85); and AHR for graft loss was 1.85 (95% CI, 1.29, 2.64). The association of UTI with death persisted after adjusting for cardiac and other infectious complications, and regardless of whether UTI was assessed as a composite of outpatient/inpatient claims, primary hospitalized UTI, or solely outpatient UTI. CONCLUSION: Whether due to a direct effect or as a marker for serious underlying illness, UTI occurring late after renal transplantation, as coded by clinicians in the United States, does not portend a benign outcome.

Chavers BM, Solid CA, Gilbertson DT, Collins AJ. Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. *J Am Soc Nephrol*. 2007; 18: 952-959.

Infection is a common cause of morbidity and mortality in patients with ESRD. Infection-related hospitalization (IH) incidence among US Medicare incident pediatric and adult dialysis and transplant patients within 3 yr of presentation was compared from 1996 to 2001: Hemodialysis (HD) patients (pediatric n = 1469; adult n = 305,323); peritoneal dialysis (PD) patients (pediatric n=982; adult n=27,119), and kidney transplant (KTx) patients (pediatric n=1108; adult n=31,663). IH were identified from principal diagnosis codes; IH cumulative incidence and rates were calculated from claims data. Cumulative incidence of IH at 36 mo for incident pediatric patients with ESRD during 1996 to 2001 was 39.9% in HD, 51.2% in PD, and 47.4% in KTx patients (HD or PD versus KTx, P<0.0001). Cumulative incidence for adults was 52.6% in HD, 51.8% in PD, and 39.8% in KTx patients (HD or PD versus KTx, P<0.0001). IH rates per 1000 patient-months were highest for pediatric KTx patients (adjusted rate ratio 1.53 versus HD and 1.90 versus PD, P<0.001 for each) and adult HD patients (adjusted rate ratio 1.20 versus KTx and 1.11 versus PD, P < 0.001 for each). Within the first 36 mo of incidence, IH rates are highest for incident pediatric KTx patients compared with HD and PD patients, in contrast to findings for adult patients with ESRD. Pediatric KTx patients require infection surveillance after transplantation.

Dharnidharka VR, Agodoa LY, Abbott KC. Effects of urinary tract infection on outcomes after renal transplantation in children. *Clin J Am Soc Nephrol*. 2007; 2: 100-106.

Urinary tract infection (UTI) is the most common infection after kidney transplantation. A previous analysis showed that late (>6 mo after transplantation) UTI is associated with earlier graft loss in adults. It was hypothesized that children who are younger than 18 yr would be at higher risk to develop UTI and develop graft loss after both early and late UTI. The US Renal Data System database was analyzed from 1996 to 2000 for Medicare claims (composite of inpatient and outpatient) for UTI up to 36 mo after transplantation. SPSS software and Cox regression models were used to determine association of UTI and age after adjustment for covariates. Early UTI was defined as occurring or =6 mo after transplantation. The risk for graft loss after early UTI was elevated in all children (adjusted hazard ratio [AHR] 5.47; 95% confidence interval [CI] 1.93 to 15.4; P < 0.001) but not after late UTI (AHR 2.09; 95% CI 0.56 to 7.80; P = 0.27). Risk for posttransplantation death was not increased significantly after either early UTI (AHR 1.23; 95% CI 0.37 to 4.08) or late UTI (relative risk 2.22; 95% CI 0.90 to 5.44). Boys aged 2 to 5 (versus age 13 to <18 years) were at significantly higher risk for UTI. In girls, only those in the youngest age category (0 to 1) had higher risk for UTI. Children are at greater risk for graft loss after early but not necessarily late UTI. UTI was not an independent predictor of death in this population.

Dharnidharka VR, Caillard S, Agodoa LY, Abbott KC. Infection frequency and profile in different age groups of kidney transplant recipients. *Transplantation*. 2006; 81(12): 1662-7.

BACKGROUND: Older transplant recipients have been shown to be at greater risk for infectious death than younger adults, but no study to date has looked at relative risk of infection and infection profile differences for children versus adults, which may be very different from one another. METHODS: Data from primary Medicare renal transplant recipients between 1991 and 1998 (n=64,751), as reported in the United States Renal Data System (USRDS), were analyzed for Medicare claims (both inpatient and outpatient) for infection and type of infection in the first year posttransplant. Cox regression was used to model adjusted hazard ratios (AHR) for infection. RESULTS: Total infections among renal transplant recipients increased significantly in more recent years. Patients transplanted in or after 1995 had a significantly higher adjusted risk for infection compared to those transplanted earlier (AHR 1.34, 95% CI=1.29-1.39). Older adults > or = 51 years of age had the highest percentage of experiencing infection, as compared to adults between 18-50 years and children < or = 17 years (P<0.001). Children were at highest risk of viral infection prior to 1995 but at lowest risk of viral infection after 1995, whereas elderly adults were at highest risk of bacterial infection throughout the study. Children experienced more claims for viral infections, whereas older transplant recipients experienced more claims for bacterial infections. CONCLUSIONS: The two extremes of transplant recipient age display very different risks for infection claim frequency and profile.

Hurst FP, Neff RT, Falta EM, et al. Incidence, predictors, and associated outcomes of prostatism after kidney transplantation. *Clin J Am Soc Nephrol*. 2009; 4: 329-336.

BACKGROUND AND OBJECTIVES: Renal transplantation is increasingly performed in elderly patients, and the incidence of benign prostatic hyperplasia (BPH) increases with age. Anuric males on dialysis may have occult BPH and not develop obstructive symptoms until urine flow is restored after transplantation. If left untreated, BPH poses a risk for numerous complications, including acute urinary retention (AUR), recurrent urinary tract infections (UTI), and renal failure. The authors hypothesized that incident BPH after renal transplantation would adversely affect allograft survival. DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: Medicare claims for BPH, AUR, UTI, and prostate resection procedures (transurethral resection of the prostate; TURP) were assessed in a retrospective cohort of 23,622 adult male Medicare primary renal transplant recipients in the

United States Renal Data System database who received transplants from 1 January 2000 to 31 July 2005 and followed through 31 December 2005. RESULTS: The 3-yr incidence of BPH post-transplant was 9.7%. The incidences of AUR, UTI, and TURP after BPH diagnosis (up to 3 yr posttransplant) were 10.3%, 6.5%, and 7.3% respectively, and each was significantly associated with BPH. Cox regression analysis showed that recipient age per year, later year of transplant, and dialysis vintage were associated with incident BPH. Using Cox nonproportional hazards regression, BPH was significantly associated with renal allograft loss (including death). CONCLUSIONS: BPH is common in males after renal transplant and is independently associated with AUR, UTI, and graft loss. It is unknown whether treatment of BPH, either medical or surgical, attenuates these risks.

Johnston O, Zalunardo N, Rose C, Gill JS. Prevention of sepsis during the transition to dialysis may improve the survival of transplant failure patients. *J Am Soc Nephrol*. 2007; 18: 1331-1337.

Dialysis patients are at risk for sepsis, and the risk may be even higher among transplant failure patients because of previous or ongoing immunosuppression. The incidence and the consequences of sepsis as defined by International Classification of Diseases, Ninth Revision, Clinical Modification hospital discharge diagnoses codes were determined among 5117 patients who initiated dialysis after transplant failure between 1995 and 2004 in the United States. The overall sepsis rate was 11.8 per 100 patient years (95% confidence interval [CI] 11.5 to 12.1). Sepsis was highest in the first 6 mo after transplant failure (35.6 per 100 patient years [95% CI 29.4 to 43.0] between 0 to 3 mo after transplant failure; 19.7 per 100 patient years [95% CI 17.2 to 22.5] between 3 to 6 mo after transplant failure). In comparison, the sepsis rate among incident dialysis patients between 3 and 6 mo after dialysis initiation was 7.8 per 100 patient years (95% CI 7.3 to 8.3), whereas the sepsis rate among transplant recipients between 3 and 6 mo after transplantation was 5.4 per 100 patient years (95% CI 4.9 to 5.9). Patients who were > or =60 yr, obese patients, patients with diabetes, and patients with a history or peripheral vascular disease or congestive heart failure were at risk for sepsis. Transplant nephrectomy was not associated with septicemia. The role of continued immunosuppression and vascular access creation was not assessed and should be addressed in future studies. In a multivariate analysis, patients who were hospitalized for sepsis had an increased risk for death (hazard ratio 2.93; 95% CI 2.64 to 3.24; $P < 0.001$). Strategies to prevent sepsis during the transition from transplantation to dialysis may improve the survival of patients with allograft failure.

Klote MM, Agodoa LY, Abbott K. Mycobacterium tuberculosis infection incidence in hospitalized renal transplant patients in the United States, 1998-2000. *Am J Transplant*. 2004; 4: 1523-1528.

The incidence, risk factors, and prognosis for Mycobacterium tuberculosis (MTB) infection have not been reported in a national population of renal transplant recipients. We performed a retrospective cohort study of 15,870 Medicare patients who received renal transplants from January 1, 1998 to July 31, 2000. Cox regression analysis derived adjusted hazard ratios (AHR) for factors associated with a diagnosis of MTB infection (by Medicare Institutional Claims) and the association of MTB infection with survival. There were 66 renal transplant recipients diagnosed with tuberculosis infection after transplant (2.5 cases per 1000 person years at risk, with some falling off of cases over time). The most common diagnosis was pulmonary TB (41 cases). In Cox regression analysis, only systemic lupus erythematosus (SLE) was independently associated with TB. Mortality after TB was diagnosed was 23% at 1 year, which was significantly higher than in renal transplant recipients without TB (AHR, 4.13, 95% CI, 2.21, 7.71, $p < 0.001$). Although uncommon, MTB infection is associated with a substantially increased risk of mortality after renal transplantation. High-risk groups, particularly those with SLE prior to transplant, might benefit from intensified screening.

Kutinova A, Woodward RS, Ricci JF, Brennan DC. The incidence and costs of sepsis and pneumonia before and after renal transplantation in the United States. *Am J Transplant*. 2006; 6: 129-139.

We compared the graft survival and accumulative costs associated with sepsis and pneumonia pre- and post-transplantation. We analyzed 44 916 first kidney transplants from 1995 to 2001 USRDS where Medicare was the primary payer. We drew five cohorts for each disease from the baseline population: patients who had a disease onset in the first or second years pre-transplantation (cohorts 1 and 2) or post-transplantation (cohorts 3 and 4) and patients who were disease-free (cohort 5). For each cohort, we calculated graft survival and average accumulated Medicare payments (AAMPs) for the two pre- and post-transplantation years. Graft survival: new-onset sepsis and pneumonia both significantly (p <0.01) lowered graft survival during the year of onset. AAMPs: the AAMPs incurred by sepsis- (pneumonia-) free patients during the first and second years post-transplantation were dollar 50,000 and 13,000 (dollar 51,100 and 13,500), respectively. Patients with a sepsis (pneumonia) onset post-transplantation cost on average dollar 48,400 (dollar 38,400) extra (p<0.01). Episodes of sepsis and pneumonia have a strong and independent impact on graft survival and costs.

Menzin J, Meyers JL, Friedman M, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. *Am J Health Syst Pharm*. 2009; 66: 1711-1717.

PURPOSE: The mortality, length of hospitalization, and costs associated with invasive fungal infections (IFIs) in hospitalized patients were studied. METHODS: This retrospective database study used data from the 2004 Healthcare Cost and Utilization Project Nationwide In-patient Sample. Patients were selected for inclusion based on diagnostic codes corresponding to an IFI. A control group was matched to the IFI group based on high-risk conditions (i.e., cancer, infection with human immunodeficiency virus, chronic obstructive pulmonary disease, diabetes mellitus, and solid-organ, hematopoietic stem cell, or bone marrow transplant), age, sex, and hospital region and teaching status. Excess mortality, length of hospital stay, and costs were estimated as the differences between the IFI and control groups. RESULTS: A total of 11,881 patients were identified with a discharge diagnosis of an IFI who could be matched to a control. Frequent infections included candidiasis (40.2%), other mycoses (36.3%), and aspergillosis (16.4%). Patients with IFIs had a significantly higher mortality rate (15% versus 5%), mean +/- S.E. length of stay (18.7 +/- 0.4 days versus 7.3 +/- 0.1 days), and mean +/- S.E. costs ($44,726 +/- $1,255 versus $15,445 +/- $404) (p < 0.001 for all comparisons) than did patients without IFIs. The burden of IFIs varied by high-risk condition (highest for transplant recipients and patients with cancer) and type of infection (highest for candidiasis, zygomycosis, and aspergillosis). CONCLUSION: Examination of a large database showed that, compared with high-risk patients without IFIs, those with IFIs had higher mortality, a longer hospital stay, and higher costs associated with their hospitalization.

Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: Incidence and risk factors for pneumocystis jiroveci pneumonia. *Transplantation*. 2009; 88: 135-141.

BACKGROUND: To investigate the effect of modern immunosuppression on the incidence, risk factors, morbidity, and mortality of Pneumocystis pneumonia (PCP) in recipients of kidney transplants. METHODS: We conducted a retrospective cohort study of 32,757 Medicare primary transplant recipients in the United States Renal Data System from January 1, 2000 through July 31, 2004. PCP infection was defined by Medicare claims using International Classification of Disease, 9th Revision codes. The incidence of PCP infections, graft loss, and death were measured. RESULTS: There were a total of 142 cases (cumulative incidence 0.4%) of PCP after kidney transplantation during the study period. By using multivariate analysis with Cox regression, expanded criteria donor,

donation after cardiac death, and earlier year of transplant were associated with development of PCP disease. Induction immunosuppression and acute rejections were not associated with risk for PCP infections. However, based on adjusted hazard ratio (AHR), maintenance immunosuppression regimens containing the combination of tacrolimus and sirolimus (AHR 3.60, confidence interval [CI] 2.03-6.39), Neoral and mycophenolate mofetil (AHR 2.09, CI 1.31-3.31), and sirolimus and mycophenolate mofetil (AHR 2.77, CI 1.40-5.47), were associated with development of PCP. As a time dependent variable, PCP was associated with an increased risk of both graft loss and death. CONCLUSION: PCP infections are rare in the modern era of prophylaxis; however, these infections are a serious risk factor for graft loss and patient death, in particular, in patients who are on sirolimus as part of the immunosuppressive regimen. The median time to development of PCP after transplant was 0.80+/-0.95 years, suggesting a longer period of PCP prophylaxis.

Rogers MA, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: A cohort study. *BMC Med*. 2009; 7: 37.

BACKGROUND: Transfusion practices in hospitalised patients are being re-evaluated, in part due to studies indicating adverse effects in patients receiving large quantities of stored blood. Concomitant with this re-examination have been reports showing variability in the use of specific blood components. This investigation was designed to assess hospital variation in blood use and outcomes in cardiac surgery patients. METHODS: We evaluated outcomes in 24,789 Medicare beneficiaries in the state of Michigan, USA who received coronary artery bypass graft surgery from 2003 to 2006. Using a cohort design, patients were followed from hospital admission to assess transfusions, in-hospital infection and mortality, as well as hospital readmission and mortality 30 days after discharge. Multilevel mixed-effects logistic regression was used to calculate the intrahospital correlation coefficient (for 40 hospitals) and compare outcomes by transfusion status. RESULTS: Overall, 30% (95 CI, 20% to 42%) of the variance in transfusion practices was attributable to hospital site. Allogeneic blood use by hospital ranged from 72.5% to 100% in women and 49.7% to 100% in men. Allogeneic, but not autologous, blood transfusion increased the odds of in-hospital infection 2.0-fold (95% CI 1.6 to 2.5), in-hospital mortality 4.7-fold (95% CI 2.4 to 9.2), 30-day readmission 1.4-fold (95% CI 1.2 to 1.6), and 30-day mortality 2.9-fold (95% CI 1.4 to 6.0) in elective surgeries. Allogeneic transfusion was associated with infections of the genitourinary system, respiratory tract, bloodstream, digestive tract and skin, as well as infection with Clostridium difficile. For each 1% increase in hospital transfusion rates, there was a 0.13% increase in predicted infection rates. CONCLUSION: Allogeneic blood transfusion was associated with an increased risk of infection at multiple sites, suggesting a system-wide immune response. Hospital variation in transfusion practices after coronary artery bypass grafting was considerable, indicating that quality efforts may be able to influence practice and improve outcomes.

Rogers MA, Blumberg N, Saint SK, Kim C, Nallamothu BK, Langa KM. Allogeneic blood transfusions explain increased mortality in women after coronary artery bypass graft surgery. *Am Heart J*. 2006; 152: 1028-1034.

BACKGROUND: Postoperative mortality is greater in women than men after coronary artery bypass graft surgery. Because allogeneic blood transfusions are more common in women and have been associated with immunomodulation, the impact of transfusion on sex differences in infection and mortality was examined. METHODS: A cohort study was conducted using Michigan Medicare beneficiaries who had undergone coronary artery bypass graft surgery. Information was used regarding allogeneic blood transfusion, infection, and mortality within the 100-day period after surgery. RESULTS: Blood transfusions were more common in women than in men (88.2%, 95% CI

87.1%-89.2% vs 66.7%, 95% CI 65.5%-67.9%). Patients who received transfused blood were more likely to have an infection than patients who did not (14.6%, 95% CI 13.8%-15.5% vs 4.9%, 95% CI 4.1%-5.9%). There was a dose-response relationship between the number of units of whole blood or packed red cells received and the prevalence of infection (P = .035). The unadjusted risk of mortality attributable to female sex was 13.9% (95% CI 8.1%-19.6%), but was no longer statistically significant when adjusted for blood transfusion (population attributable risk 0.6%, 95% CI -6.0% to 6.6%). Patients who received a transfusion were 5.6 times as likely to die within 100 days after surgery as those who did not receive a transfusion (95% CI 3.7-8.6). CONCLUSION: The increased risk of mortality in women after bypass surgery may be explained by transfusion-related immunosuppression.

Shroff GR, Skeans M, Herzog CA. Outcomes of renal transplant and waiting list patients with bacterial endocarditis in the United States. *Nephrol Dial Transplant*. 2008; 23: 2381-2385.

BACKGROUND: Bacterial endocarditis is associated with poor long-term survival among dialysis patients. Renal transplant patients and those waiting list for renal transplantation are predisposed to developing bacterial endocarditis; data regarding incidence and outcomes are limited. METHODS: Patients hospitalised for bacterial endocarditis were identified from patients transplanted or waiting list between 1995 and 2003. Transplant and waiting list cohorts were derived from the United States Renal Data System (USRDS) database. All patients had Medicare as primary payer. Long-term survival was estimated by the Kaplan-Meier method. Cox proportional hazards analysis was used to identify independent predictors of bacterial endocarditis. RESULTS: During the study period, 282 renal transplant patients and 549 waiting list patients were hospitalised with bacterial endocarditis. Incidence rates of bacterial endocarditis per 1000 patient-years were 5.6 among waiting list patients, 2.6 among deceased-donor transplant recipients and 1.8 among living-donor transplant recipients. In-hospital mortality rates were 16.0% for the renal transplant cohort and 18.6% for the waiting list cohort. Two-year post-endocarditis survival rates were 58% for transplant patients and 41% for waiting list patients. The most powerful predictors of bacterial endocarditis among transplant patients were donor age, patient age, diabetic end-stage renal disease (ESRD) and prior dialysis time longer than 2 years. CONCLUSIONS: Renal transplant patients hospitalised with bacterial endocarditis sustain high in-hospital and long-term mortality rates. Waiting list patients are at higher risk of developing bacterial endocarditis than renal transplant recipients.

Snyder JJ, Israni AK, Peng Y, Zhang L, Simon TA, Kasiske BL. Rates of first infection following kidney transplant in the United States. *Kidney Int*. 2009; 75: 317-326.

We studied the incidence, trends and clinical correlates of infections following kidney transplantation in the United States Renal Data System over the years 1995-2003 in 46,471 adults with Medicare primary coverage at the time of their first kidney transplant. The incidence of most infections has declined only slightly since 1995 but infection with cytomegalovirus significantly declined while that with hepatitis C significantly increased. Relative frequencies of different types of infections (bacterial, viral, fungal and parasitic) were relatively constant, both during early and late periods following transplant. Using the Cox proportional hazards analysis we found that the clinical correlates for post-transplant bacterial and viral infections included older age, female gender, diabetes as the cause of end-stage renal disease, deceased (vs living) donor source, time on dialysis before transplant, hepatitis B and C viral pre-transplant serologic status and pre-transplant donor-recipient cytomegalovirus serology. Our study shows that despite identifiable risk factors, the incidence of most post-transplant infections has changed little since 1995.

Tong KB, Lau CJ, Murtagh K, Layton AJ, Seifeldin R. The economic impact of aspergillosis: Analysis of hospital expenditures across patient subgroups. *Int J Infect Dis*. 2009; 13: 24-36.

OBJECTIVE: To measure the impact of invasive aspergillosis infection on US hospital costs and financial performance across different patient populations. METHODS: Hospital discharge data for patients with a primary or secondary diagnosis of aspergillosis were extracted from the 2003 Nationwide Inpatient Sample (NIS) and the fiscal year 2003 (FYO3) Medicare Provider Analysis and Review (MedPAR) file. The data on patient demographics, length of stay (LOS), hospital charges, estimated costs, and reimbursement levels were reported. After controlling for comorbidities, operative procedures, and diagnosis-related group (DRG) assignment, the clinical and economic outcomes were compared for patients with and without aspergillosis. RESULTS: The NIS contains a total of over 38 million projected hospital discharges. From these, 10400 aspergillosis cases were identified across 171 DRGs, resulting in a US incidence rate of 36 per million per year. The mean age of aspergillosis patients was 55.6 years, with 53.4% male and 67.9% Caucasian. The median (mean) LOS per aspergillosis patient was 10 (17.7) days, with a median (mean) total hospital charge (THC) of $44,845 ($96,731). Among the patient subgroups analyzed, the median (mean) THC per patient ranged from $47,252 ($82,946) for HIV to $413,200 ($442,233) for bone marrow transplant (BMT). When compared to the non-aspergillosis patient population, the data showed a significant increase in LOS, THC, and hospital costs. Furthermore, the higher hospital costs associated with aspergillosis patients were not matched by similar increases in reimbursements, resulting in a greater financial loss for hospitals. The mean reimbursement-to-cost ratio for aspergillosis cases across the DRGs analyzed was 0.80. CONCLUSIONS: Aspergillosis affects a wide range of patient groups and has a negative economic impact across many DRGs. Improved prevention, diagnosis, and patient management strategies can help mitigate these effects on hospital financial performance.

B. APPENDIX B: LIST OF CITATIONS SELECTED FOR FULL-TEXT REVIEW BUT NOT INCLUDED, BY REASONS FOR EXCLUSION

1. Studies Excluded Because They Did Not Study the HOI

Abbott KC, Bucci JR, Matsumoto CS, et al. Hepatitis C and renal transplantation in the era of modern immunosuppression. *J Am Soc Nephrol*. 2003; 14(11): 2908-2918.

Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: A cost-utility analysis. *Am J Gastroenterol*. 2003; 98(3): 679-690.

Busch MP, Switzer WM, Murphy EL, Thomson R, Heneine W. Absence of evidence of infection with divergent primate T-lymphotropic viruses in United States blood donors who have seroindeterminate HTLV test results. *Transfusion*. 2000; 40(4): 443-449.

Butt AA, Skanderson M, McGinnis KA, et al. Impact of hepatitis C virus infection and other comorbidities on survival in patients on dialysis. *J Viral Hepat*. 2007; 14(10): 688-696.

Campos-Lobato LF, Wells B, Wick E, et al. Predicting organ space surgical site infection with a nomogram. *J Gastrointest Surg*. 2009; 13(11): 1986-1992.

Cocco PL, Caperna A, Vinci F. Occupational risk factors for the sporadic form of creutzfeldt-jakob disease. *Med Lav*. 2003; 94(4): 353-363.

El-Serag HB, Anand B, Richardson P, Rabeneck L. Association between hepatitis C infection and other infectious diseases: A case for targeted screening? *Am J Gastroenterol*. 2003; 98(1): 167-174.

Greenblatt DY, Weber SM, O'Connor ES, LoConte NK, Liou JI, Smith MA. Readmission after colectomy for cancer predicts one-year mortality. *Ann Surg*. 2010; 251(4): 659-669.

Gupta M, Shanley TP, Moler FW. Extracorporeal life support for severe respiratory failure in children with immune compromised conditions. *Pediatr Crit Care Med*. 2008; 9(4): 380-385.

Henke PK, Blackburn SA, Wainess RW, et al. Osteomyelitis of the foot and toe in adults is a surgical disease: Conservative management worsens lower extremity salvage. *Ann Surg*. 2005; 241(6): 885-92, discussion 892-4.

Juillard C, Lashoher A, Sewell CA, Uddin S, Griffith JG, Chang DC. A national analysis of the relationship between hospital volume, academic center status, and surgical outcomes for abdominal hysterectomy done for leiomyoma. *J Am Coll Surg*. 2009; 208(4): 599-606.

McAllister DR, Parker RD, Cooper AE, Recht MP, Abate J. Outcomes of postoperative septic arthritis after anterior cruciate ligament reconstruction. *Am J Sports Med*. 1999; 27(5): 562-570.

Murphy EL, Bryzman SM, Glynn SA, et al. Risk factors for hepatitis C virus infection in United States blood donors. NHLBI Retrovirus Epidemiology Donor Study (REDS). *Hepatology*. 2000; 31(3): 756-762.

Scanlon MC, Harris JM,2nd, Levy F, Sedman A. Evaluation of the agency for healthcare research and quality pediatric quality indicators. *Pediatrics*. 2008; 121(6): e1723-31.

Shah T, Kasravi A, Huang E, et al. Risk factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation*. 2006; 82(12): 1673-1676.

2. Studies Excluded Because They Did Not Use an Administrative Database

Current good manufacturing practices for blood and blood components: Notification of consignees receiving blood and blood components at increased risk for transmitting HIV infection--FDA. Final rule. *Fed Regist*. 1996; 61(175): 47413-47423.

Aduen JF, Sujay B, Dickson RC, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. *Mayo Clin Proc*. 2009; 84(11): 973-978.

Afessa B, Tefferi A, Hoagland HC, Letendre L, Peters SG. Outcome of recipients of bone marrow transplants who require intensive-care unit support. *Mayo Clin Proc*. 1992; 67(2): 117-122.

Al-Hasan MN, Razonable RR, Eckel-Passow JE, Baddour LM. Incidence rate and outcome of gram-negative bloodstream infection in solid organ transplant recipients. *Am J Transplant*. 2009; 9(4): 835-843.

Arness T, Pedersen R, Dierkhising R, Kremers W, Patel R. Varicella zoster virus-associated disease in adult kidney transplant recipients: Incidence and risk-factor analysis. *Transpl Infect Dis*. 2008; 10(4): 260-268.

Bajjoka I, Hsaiky L, Brown K, Abouljoud M. Preserving renal function in liver transplant recipients with rabbit anti-thymocyte globulin and delayed initiation of calcineurin inhibitors. *Liver Transpl*. 2008; 14(1): 66-72.

Bell CE, Botteman MF, Gao X, et al. Cost-effectiveness of transfusion of platelet components prepared with pathogen inactivation treatment in the United States. *Clin Ther*. 2003; 25(9): 2464-2486.

Bower TC, Nagorney DM, Cherry KJ,Jr, et al. Replacement of the inferior vena cava for malignancy: An update. *J Vasc Surg*. 2000; 31(2): 270-281.

Bozzette SA, Parker R, Hay J. A cost analysis of approved antiretroviral strategies in persons with advanced human immunodeficiency virus disease and zidovudine intolerance. *J Acquir Immune Defic Syndr*. 1994; 7(4): 355-362.

Braddy CM, Heilman RL, Blair JE. Coccidioidomycosis after renal transplantation in an endemic area. *Am J Transplant*. 2006; 6(2): 340-345.

Brandhagen DJ, Gross JB,Jr, Poterucha JJ, et al. The clinical significance of simultaneous infection with hepatitis G virus in patients with chronic hepatitis C. *Am J Gastroenterol*. 1999; 94(4): 1000-1005.

Brewer JD, Colegio OR, Phillips PK, et al. Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol*. 2009; 145(12): 1391-1396.

Camporota L, Corno E, Menaldo E, et al. Filter survival time and requirement of blood products in patients with severe sepsis receiving drotrecogin alfa (activated) and requiring renal replacement therapy. *Crit Care*. 2008; 12(6): R163.

Cantoni N, Weisser M, Buser A, et al. Infection prevention strategies in a stem cell transplant unit: Impact of change of care in isolation practice and routine use of high dose intravenous immunoglobulins on infectious complications and transplant related mortality. *Eur J Haematol*. 2009; 83(2): 130-138.

Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion*. 1999; 39(7): 694-700.

Charlton MR, Brandhagen D, Wiesner RH, et al. Hepatitis G virus infection in patients transplanted for cryptogenic cirrhosis: Red flag or red herring? *Transplantation*. 1998; 65(1): 73-76.

Cheung RC. Epidemiology of hepatitis C virus infection in American veterans. *Am J Gastroenterol*. 2000; 95(3): 740-747.

Cooper WA, O'Brien SM, Thourani VH, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: Results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation*. 2006; 113(8): 1063-1070.

Copp DH, Godwin JD, Kirby KA, Limaye AP. Clinical and radiologic factors associated with pulmonary nodule etiology in organ transplant recipients. *Am J Transplant*. 2006; 6(11): 2759-2764.

Crocker JF, Wade AW, McDonald AT, et al. Kidney graft loss in children: Implications for program development. *CMAJ*. 1998; 159(3): 229-235.

Danziger-Isakov LA, Sweet S, Delamorena M, Huddleston CB, Mendeloff E, Debaun MR. Epidemiology of bloodstream infections in the first year after pediatric lung transplantation. *Pediatr Infect Dis J*. 2005; 24(4): 324-330.

Danziger-Isakov LA, Worley S, Arrigain S, et al. Increased mortality after pulmonary fungal infection within the first year after pediatric lung transplantation. *J Heart Lung Transplant*. 2008; 27(6): 655-661.

Danziger-Isakov LA, Worley S, Michaels MG, et al. The risk, prevention, and outcome of cytomegalovirus after pediatric lung transplantation. *Transplantation*. 2009; 87(10): 1541-1548.

Delgado J, Pillai S, Benjamin R, et al. The effect of in vivo T cell depletion with alemtuzumab on reduced-intensity allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia. *Biol Blood Marrow Transplant*. 2008; 14(11): 1288-1297.

Dockrell DH, Mendez JC, Jones M, et al. Human herpesvirus 6 seronegativity before transplantation predicts the occurrence of fungal infection in liver transplant recipients. *Transplantation*. 1999; 67(3): 399-403.

Dominitz JA, Boyko EJ, Koepsell TD, et al. Elevated prevalence of hepatitis C infection in users of United States veterans medical centers. *Hepatology*. 2005; 41(1): 88-96.

Duclos AJ, Krishnamurthi V, Lard M, et al. Prevalence and clinical course of BK virus nephropathy in pancreas after kidney transplant patients. *Transplant Proc*. 2006; 38(10): 3666-3672.

Dunne JR, Malone D, Tracy JK, Gannon C, Napolitano LM. Perioperative anemia: An independent risk factor for infection, mortality, and resource utilization in surgery. *J Surg Res*. 2002; 102(2): 237-244.

Garbino J, Gerbase MW, Wunderli W, et al. Respiratory viruses and severe lower respiratory tract complications in hospitalized patients. *Chest*. 2004; 125(3): 1033-1039.

Garwood RA, Sawyer RG, Thompson L, Adams RB. Infectious complications after hepatic resection. *Am Surg*. 2004; 70(9): 787-792.

Gertz MA, Lacy MQ, Dispenzieri A, et al. Transplantation without growth factor: Engraftment kinetics after stem cell transplantation for primary systemic amyloidosis (AL). *Bone Marrow Transplant*. 2007; 40(10): 989-993.

Ghabril M, Dickson R, Wiesner R. Improving outcomes of liver retransplantation: An analysis of trends and the impact of hepatitis C infection. *Am J Transplant*. 2008; 8(2): 404-411.

Ghabril M, Dickson RC, Krishna M, et al. Liver transplantation using young pediatric donor grafts in adults with hepatitis C infection. *Transplantation*. 2009; 87(8): 1174-1179.

Ghabril M, Dickson RC, Machicao VI, et al. Liver retransplantation of patients with hepatitis C infection is associated with acceptable patient and graft survival. *Liver Transpl*. 2007; 13(12): 1717-1727.

Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Siracuse JJ, Schermerhorn ML. Body mass index: Surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005-2007. *Ann Vasc Surg*. 2010; 24(1): 48-56.

Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. *Transplantation*. 2001; 71(2): 242-246.

Gonzalez-Stawinski GV, Cook DJ, Chang AS, et al. Ventricular assist devices and aggressive immunosuppression: Looking beyond overall survival. *J Heart Lung Transplant*. 2006; 25(6): 613-618.

Grady KL, White-Williams C, Naftel D, et al. Are preoperative obesity and cachexia risk factors for post heart transplant morbidity and mortality: A multi-institutional study of preoperative

weight-height indices. Cardiac Transplant Research Database (CTRD) group. *J Heart Lung Transplant*. 1999; 18(8): 750-763.

Graff LR, Franklin KK, Witt L, et al. Antimicrobial therapy of gram-negative bacteremia at two university-affiliated medical centers. *Am J Med*. 2002; 112(3): 204-211.

Graziadei IW, Wiesner RH, Marotta PJ, et al. Long-term results of patients undergoing liver transplantation for primary sclerosing cholangitis. *Hepatology*. 1999; 30(5): 1121-1127.

Guo L, Orrego M, Rodriguez-Luna H, et al. Living donor liver transplantation for hepatitis C-related cirrhosis: No difference in histological recurrence when compared to deceased donor liver transplantation recipients. *Liver Transpl*. 2006; 12(4): 560-565.

Gupta S, Mitchell JD, Markham DW, et al. Utility of the cylex assay in cardiac transplant recipients. *J Heart Lung Transplant*. 2008; 27(8): 817-822.

Hanrahan JS, Eberly C, Mohanty PK. Substance abuse in heart transplant recipients: A 10-year follow-up study. *Prog Transplant*. 2001; 11(4): 285-290.

Harold K, Mekeel K, Spitler J, et al. Outcomes analysis of laparoscopic ventral hernia repair in transplant patients. *Surg Endosc*. 2009; 23(8): 1835-1838.

Heisler CA, Casiano ER, Gebhart JB. Hysterectomy and perioperative morbidity in women who have undergone renal transplantation. *Am J Obstet Gynecol*. 2010; 202(3): 314.e1-314.e4.

Hellinger WC, Bonatti H, Yao JD, et al. Risk stratification and targeted antifungal prophylaxis for prevention of aspergillosis and other invasive mold infections after liver transplantation. *Liver Transpl*. 2005; 11(6): 656-662.

Hellinger WC, Crook JE, Heckman MG, et al. Surgical site infection after liver transplantation: Risk factors and association with graft loss or death. *Transplantation*. 2009; 87(9): 1387-1393.

Hennessy SA, Hranjec T, Swenson BR, et al. Donor factors are associated with bronchiolitis obliterans syndrome after lung transplantation. *Ann Thorac Surg*. 2010; 89(5): 1555-1562.

Hurwitz M, Desai DM, Cox KL, Berquist WE, Esquivel CO, Millan MT. Complete immunosuppressive withdrawal as a uniform approach to post-transplant lymphoproliferative disease in pediatric liver transplantation. *Pediatr Transplant*. 2004; 8(3): 267-272.

Husni RN, Gordon SM, Longworth DL, et al. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. *Clin Infect Dis*. 1998; 26(3): 753-755.

Ito JI, Chandrasekar PH, Hooshmand-Rad R. Effectiveness of amphotericin B lipid complex (ABLC) treatment in allogeneic hematopoietic cell transplant (HCT) recipients with invasive aspergillosis (IA). *Bone Marrow Transplant*. 2005; 36(10): 873-877.

Jones KW, Cain AS, Mitchell JH, et al. Hyperglycemia predicts mortality after CABG: Postoperative hyperglycemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. *J Diabetes Complications*. 2008; 22(6): 365-370.

Kelso RL, Lyden SP, Butler B, Greenberg RK, Eagleton MJ, Clair DG. Late conversion of aortic stent grafts. *J Vasc Surg*. 2009; 49(3): 589-595.

Kim MS, Stablein D, Harmon WE. Renal transplantation in children with congenital nephrotic syndrome: A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Pediatr Transplant*. 1998; 2(4): 305-308.

Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008; 358(12): 1229-1239.

Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. *Blood*. 2000; 95(12): 3683-3686.

Kurbegov AC, Sondheimer JM. Pneumatosis intestinalis in non-neonatal pediatric patients. *Pediatrics*. 2001; 108(2): 402-406.

Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD. Hepatitis C infection risk analysis: Who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. *Am J Gastroenterol*. 1998; 93(4): 591-596.

Lee ES, Santilli SM, Olson MM, Kuskowski MA, Lee JT. Wound infection after infrainguinal bypass operations: Multivariate analysis of putative risk factors. *Surg Infect (Larchmt)*. 2000; 1(4): 257-263.

Liu M, Worley S, Arrigain S, et al. Respiratory viral infections within one year after pediatric lung transplant. *Transpl Infect Dis*. 2009; 11(4): 304-312.

Liu M, Worley S, Mallory GB,Jr, et al. Fungal infections in pediatric lung transplant recipients: Colonization and invasive disease. *J Heart Lung Transplant*. 2009; 28(11): 1226-1230.

Lytle BW, Sabik JF, Blackstone EH, Svensson LG, Pettersson GB, Cosgrove DM,3rd. Reoperative cryopreserved root and ascending aorta replacement for acute aortic prosthetic valve endocarditis. *Ann Thorac Surg*. 2002; 74(5): S1754-7, discussion S1792-9.

Mamoun NF, Xu M, Sessler DI, Sabik JF, Bashour CA. Propensity matched comparison of outcomes in older and younger patients after coronary artery bypass graft surgery. *Ann Thorac Surg*. 2008; 85(6): 1974-1979.

Manuel O, Venetz JP, Fellay J, et al. Efficacy and safety of universal valganciclovir prophylaxis combined with a tacrolimus/mycophenolate-based regimen in kidney transplantation. *Swiss Med Wkly*. 2007; 137(47-48): 669-676.

Marelli D, Laks H, Patel B, et al. Heart transplantation in patients with diabetes mellitus in the current era. *J Heart Lung Transplant*. 2003; 22(10): 1091-1097.

Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2002; 34(7): 909-917.

Mattox TF, Stanford EJ, Varner E. Infected abdominal sacrocolpopexies: Diagnosis and treatment. *Int Urogynecol J Pelvic Floor Dysfunct*. 2004; 15(5): 319-323.

McGrath T, Koch CG, Xu M, et al. Platelet transfusion in cardiac surgery does not confer increased risk for adverse morbid outcomes. *Ann Thorac Surg*. 2008; 86(2): 543-553.

Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B. Hepatitis C antibody status and outcomes in renal transplant recipients. *Transplantation*. 2001; 72(2): 241-244.

Mertens RA, O'Hara PJ, Hertzer NR, Krajewski LP, Beven EG. Surgical management of infrainguinal arterial prosthetic graft infections: Review of a thirty-five-year experience. *J Vasc Surg*. 1995; 21(5): 782-90, discussion 790-1.

Mikhael MM, Huddleston PM, Nassr A. Postoperative culture positive surgical site infections after the use of irradiated allograft, nonirradiated allograft, or autograft for spinal fusion. *Spine (Phila Pa 1976)*. 2009; 34(22): 2466-2468.

Mossad SB, Longworth DL, Goormastic M, Serkey JM, Keys TF, Bolwell BJ. Early infectious complications in autologous bone marrow transplantation: A review of 219 patients. *Bone Marrow Transplant*. 1996; 18(2): 265-271.

Mulaudzi TV, Robbs JV, Paruk N, Pillay B, Madiba TE, Govindsamy V. The influence of diabetes on short-term outcome following a prosthetic above-the-knee femoro-popliteal bypass. *Cardiovasc J Afr*. 2009; 20(3): 170-172.

Nassr A, Khan MH, Ali MH, et al. Donor-site complications of autogenous nonvascularized fibula strut graft harvest for anterior cervical corpectomy and fusion surgery: Experience with 163 consecutive cases. *Spine J*. 2009; 9(11): 893-898.

Noel AA, Gloviczki P, Cherry KJ,Jr, et al. Abdominal aortic reconstruction in infected fields: Early results of the United States Cryopreserved Aortic Allograft Registry. *J Vasc Surg*. 2002; 35(5): 847-852.

Oderich GS, Bower TC, Cherry KJ,Jr, et al. Evolution from axillofemoral to in situ prosthetic reconstruction for the treatment of aortic graft infections at a single center. *J Vasc Surg*. 2006; 43(6): 1166-1174.

Oderich GS, Panneton JM, Cherry KJ,Jr, et al. Carotid artery reconstruction combined with myocutaneous flap coverage: A complex and durable rescue operation. *Ann Vasc Surg*. 2002; 16(5): 579-585.

O'Hare AM, Feinglass J, Sidawy AN, et al. Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: Data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol*. 2003; 14(5): 1287-1295.

O'Keeffe SD, Davenport DL, Minion DJ, Sorial EE, Endean ED, Xenos ES. Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. *J Vasc Surg*. 2010; 51(3): 616-21, 621.e1-3.

Onaca NN, Levy MF, Netto GJ, et al. Pretransplant MELD score as a predictor of outcome after liver transplantation for chronic hepatitis C. *Am J Transplant*. 2003; 3(5): 626-630.

Ong JP, Barnes DS, Younossi ZM, et al. Outcome of de novo hepatitis C virus infection in heart transplant recipients. *Hepatology*. 1999; 30(5): 1293-1298.

Orloff SL, Busch AM, Olyaei AJ, et al. Vancomycin-resistant enterococcus in liver transplant patients. *Am J Surg*. 1999; 177(5): 418-422.

Palmer JA, Kaiser BA, Polinsky MS, et al. Peritoneal dialysis catheter infections in children after renal transplantation: Choosing the time of removal. *Pediatr Nephrol*. 1994; 8(6): 715-718.

Palmer SM, Alexander BD, Sanders LL, et al. Significance of blood stream infection after lung transplantation: Analysis in 176 consecutive patients. *Transplantation*. 2000; 69(11): 2360-2366.

Patel R. Vancomycin-resistant enterococci in liver transplant recipients. *Liver Transpl*. 2000; 6(2): 247-249.

Poonyagariyagorn HK, Gershman A, Avery R, et al. Challenges in the diagnosis and management of nocardia infections in lung transplant recipients. *Transpl Infect Dis*. 2008; 10(6): 403-408.

Pourfarziani V, Rafati-Shaldehi H, Assari S, et al. Hospitalization databases: A tool for transplantation monitoring. *Transplant Proc*. 2007; 39(4): 981-983.

Powe NR, Griffiths RI, Bass EB. Cost implications to Medicare of recombinant erythropoietin therapy for the anemia of end-stage renal disease. *J Am Soc Nephrol*. 1993; 3(10): 1660-1671.

Rabkin JM, de La Melena V, Orloff SL, Corless CL, Rosen HR, Olyaei AJ. Late mortality after orthotopic liver transplantation. *Am J Surg*. 2001; 181(5): 475-479.

Rabkin JM, Oroloff SL, Corless CL, et al. Association of fungal infection and increased mortality in liver transplant recipients. *Am J Surg*. 2000; 179(5): 426-430.

Rhodes JM, Cherry KJ,Jr, Clark RC, et al. Aortic-origin reconstruction of the great vessels: Risk factors of early and late complications. *J Vasc Surg*. 2000; 31(2): 260-269.

Robertson JO, Lober C, Smedira NG, Navia JL, Sopko N, Gonzalez-Stawinski GV. One hundred days or more bridged on a ventricular assist device and effects on outcomes following heart transplantation. *Eur J Cardiothorac Surg*. 2008; 34(2): 295-300.

Roddie C, Paul JP, Benjamin R, et al. Allogeneic hematopoietic stem cell transplantation and norovirus gastroenteritis: A previously unrecognized cause of morbidity. *Clin Infect Dis*. 2009; 49(7): 1061-1068.

Rodriguez-Luna H, Balan V, Sharma P, et al. Hepatitis C virus infection with hepatocellular carcinoma: Not a controversial indication for liver transplantation. *Transplantation*. 2004; 78(4): 580-583.

Rosen HR, Chou S, Corless CL, et al. Cytomegalovirus viremia: Risk factor for allograft cirrhosis after liver transplantation for hepatitis C. *Transplantation*. 1997; 64(5): 721-726.

Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. *Transplantation*. 1998; 66(12): 1612-1616.

Rosenbaum DH, Adams BC, Mitchell JD, et al. Effects of early steroid withdrawal after heart transplantation. *Ann Thorac Surg*. 2006; 82(2): 637-44, discussion 644.

Rostambeigi N, Kudva YC, John S, et al. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. *Transplantation*. 2010; 89(9): 1126-1133.

Rothwell WS, Gloor JM, Morgenstern BZ, Milliner DS. Disseminated varicella infection in pediatric renal transplant recipients treated with mycophenolate mofetil. *Transplantation*. 1999; 68(1): 158-161.

Salvadori M, Bock A, Chapman J, et al. Impact of mycophenolate mofetil dose posttransplantation on 12-month renal function: Analysis of the MOST database. *Transplant Proc*. 2005; 37(6): 2464-2466.

Sandhu J, Preiksaitis JK, Campbell PM, Carriere KC, Hessel PA. Hepatitis C prevalence and risk factors in the northern Alberta dialysis population. *Am J Epidemiol*. 1999; 150(1): 58-66.

Sarmiento JM, Dockrell DH, Schwab TR, Munn SR, Paya CV. Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. *Clin Transplant*. 2000; 14(2): 136-138.

Sarmiento JM, Munn SR, Paya CV, Velosa JA, Nguyen JH. Is cytomegalovirus infection related to mycophenolate mofetil after kidney transplantation? A case-control study. *Clin Transplant*. 1998; 12(5): 371-374.

Sasaki H, Mitchell JD, Jessen ME, et al. Bridge to heart transplantation with left ventricular assist device versus inotropic agents in status 1 patients. *J Card Surg*. 2009; 24(6): 756-762.

Sauaia A, Alexander W, Moore EE, Stevens BR, Rosen H, Dunn TR. Autologous blood transfusion does not reduce postoperative infection rates in elective surgery. *Am J Surg*. 1999; 178(6): 549-555.

Schaenman JM, Rosso F, Austin JM, et al. Trends in invasive disease due to candida species following heart and lung transplantation. *Transpl Infect Dis*. 2009; 11(2): 112-121.

Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 3--valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009; 88(1 Suppl): S43-62.

Singh N. Cytomegalovirus infection of liver transplant recipients: Comparison of antigenemia and molecular biology assays. *Liver Transpl*. 2001; 7(11): 1004-1007.

Singh N, Chang FY, Gayowski T, Wagener M, Marino IR. Fever in liver transplant recipients in the intensive care unit. *Clin Transplant*. 1999; 13(6): 504-511.

Singh N, Gayowski T, Wagener MM. Posttransplantation dialysis-associated infections: Morbidity and impact on outcome in liver transplant recipients. *Liver Transpl*. 2001; 7(2): 100-105.

Singh N, Gayowski T, Wagener MM, Marino IR. Predictors and outcome of early- versus late-onset major bacterial infections in liver transplant recipients receiving tacrolimus (FK506) as primary immunosuppression. *Eur J Clin Microbiol Infect Dis*. 1997; 16(11): 821-826.

Singh N, Paterson DL, Chang FY, et al. Methicillin-resistant staphylococcus aureus: The other emerging resistant gram-positive coccus among liver transplant recipients. *Clin Infect Dis*. 2000; 30(2): 322-327.

Singh N, Paterson DL, Gayowski T, Wagener MM, Marino IR. Preemptive prophylaxis with a lipid preparation of amphotericin B for invasive fungal infections in liver transplant recipients requiring renal replacement therapy. *Transplantation*. 2001; 71(7): 910-913.

Singh N, Wagener MM, Obman A, Cacciarelli TV, de Vera ME, Gayowski T. Bacteremias in liver transplant recipients: Shift toward gram-negative bacteria as predominant pathogens. *Liver Transpl*. 2004; 10(7): 844-849.

Singh N, Wannstedt C, Keyes L, Gayowski T, Wagener MM, Cacciarelli TV. Efficacy of valganciclovir administered as preemptive therapy for cytomegalovirus disease in liver transplant recipients: Impact on viral load and late-onset cytomegalovirus disease. *Transplantation*. 2005; 79(1): 85-90.

Singh N, Wannstedt C, Keyes L, et al. Impact of evolving trends in recipient and donor characteristics on cytomegalovirus infection in liver transplant recipients. *Transplantation*. 2004; 77(1): 106-110.

Singh N, Wannstedt C, Keyes L, Wagener MM, Gayowski T, Cacciarelli TV. Indirect outcomes associated with cytomegalovirus (opportunistic infections, hepatitis C virus sequelae, and

mortality) in liver-transplant recipients with the use of preemptive therapy for 13 years. *Transplantation*. 2005; 79(10): 1428-1434.

Smart FW, Naftel DC, Costanzo MR, et al. Risk factors for early, cumulative, and fatal infections after heart transplantation: A multiinstitutional study. *J Heart Lung Transplant*. 1996; 15(4): 329-341.

Smith S, Mountcastle S, Burridge A, et al. A single-institution experience with the AneuRx stent graft for endovascular repair of abdominal aortic aneurysm. *Ann Vasc Surg*. 2008; 22(2): 221-226.

Squier C, Rihs JD, Risa KJ, et al. Staphylococcus aureus rectal carriage and its association with infections in patients in a surgical intensive care unit and a liver transplant unit. *Infect Control Hosp Epidemiol*. 2002; 23(9): 495-501.

Svensson LG, Mumtaz MA, Blackstone EH, et al. Does use of a right internal thoracic artery increase deep wound infection and risk after previous use of a left internal thoracic artery? *J Thorac Cardiovasc Surg*. 2006; 131(3): 609-613.

Tabbara MR, O'Hara PJ, Hertzer NR, Krajewski LP, Beven EG. Surgical management of infected PTFE hemodialysis grafts: Analysis of a 15-year experience. *Ann Vasc Surg*. 1995; 9(4): 378-384.

Tachopoulou OA, Vogt DP, Henderson JM, Baker M, Keys TF. Hepatic abscess after liver transplantation: 1990-2000. *Transplantation*. 2003; 75(1): 79-83.

Taylor DO, Bristow MR, O'Connell JB, et al. Improved long-term survival after heart transplantation predicted by successful early withdrawal from maintenance corticosteroid therapy. *J Heart Lung Transplant*. 1996; 15(10): 1039-1046.

Thomson KJ, Hart DP, Banerjee L, Ward KN, Peggs KS, Mackinnon S. The effect of low-dose aciclovir on reactivation of varicella zoster virus after allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005; 35(11): 1065-1069.

Tretiak R, Laupacis A, Riviere M, McKerracher K, Souetre E. Cost of allogeneic and autologous blood transfusion in Canada. Canadian cost of transfusion study group. *CMAJ*. 1996; 154(10): 1501-1508.

Trulock EP, Ettinger NA, Brunt EM, Pasque MK, Kaiser LR, Cooper JD. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. *Chest*. 1992; 102(4): 1049-1054.

Tsao L, Uriel N, Leitz K, Naka Y, Mancini D. Higher rate of comorbidities after cardiac retransplantation contributes to decreased survival. *J Heart Lung Transplant*. 2009; 28(10): 1072-1074.

Tyndall SH, Shepard AD, Wilczewski JM, Reddy DJ, Elliott JP,Jr, Ernst CB. Groin lymphatic complications after arterial reconstruction. *J Vasc Surg*. 1994; 19(5): 858-63, discussion 863-4.

van Burik JA, Lawatsch EJ, DeFor TE, Weisdorf DJ. Cytomegalovirus enteritis among hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2001; 7(12): 674-679.

van de Beek D, Kremers WK, Del Pozo JL, et al. Effect of infectious diseases on outcome after heart transplant. *Mayo Clin Proc*. 2008; 83(3): 304-308.

van de Beek D, Patel R, Daly RC, McGregor CG, Wijdicks EF. Central nervous system infections in heart transplant recipients. *Arch Neurol*. 2007; 64(12): 1715-1720.

Van Kamp IL, Klumper FJ, Oepkes D, et al. Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. *Am J Obstet Gynecol*. 2005; 192(1): 171-177.

Veldt BJ, Poterucha JJ, Watt KD, et al. Impact of pegylated interferon and ribavirin treatment on graft survival in liver transplant patients with recurrent hepatitis C infection. *Am J Transplant*. 2008; 8(11): 2426-2433.

Wang A, Book WM, McConnell M, Lyle T, Rodby K, Mahle WT. Prevalence of hepatitis C infection in adult patients who underwent congenital heart surgery prior to screening in 1992. *Am J Cardiol*. 2007; 100(8): 1307-1309.

Wiesner RH, Shorr JS, Steffen BJ, Chu AH, Gordon RD, Lake JR. Mycophenolate mofetil combination therapy improves long-term outcomes after liver transplantation in patients with and without hepatitis C. *Liver Transpl*. 2005; 11(7): 750-759.

Wutoh AK, Hidalgo J, Rhee W, Bareta J. A characterization of older AIDS patients in Maryland. *J Natl Med Assoc*. 1998; 90(6): 369-373.

Yamani MH, Chuang HH, Ozduran V, et al. The impact of hypogammaglobulinemia on infection outcome in patients undergoing ventricular assist device implantation. *J Heart Lung Transplant*. 2006; 25(7): 820-824.

Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: Primary graft nonfunction and hepatitis C virus are associated with worse outcome. *Liver Transpl*. 2003; 9(9): 897-904.

Young RM, Cherry KJ,Jr, Davis PM, et al. The results of in situ prosthetic replacement for infected aortic grafts. *Am J Surg*. 1999; 178(2): 136-140.

Younossi ZM, Braun WE, Protiva DA, Gifford RW,Jr, Straffon RA. Chronic viral hepatitis in renal transplant recipients with allografts functioning for more than 20 years. *Transplantation*. 1999; 67(2): 272-275.

Zirakzadeh A, Gastineau DA, Mandrekar JN, Burke JP, Johnston PB, Patel R. Vancomycin-resistant enterococcal colonization appears associated with increased mortality among allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2008; 41(4): 385-392.

Zuppan CW, Wells LM, Kerstetter JC, Johnston JK, Bailey LL, Chinnock RE. Cause of death in pediatric and infant heart transplant recipients: Review of a 20-year, single-institution cohort. *J Heart Lung Transplant*. 2009; 28(6): 579-584.

3. Studies Excluded Due to Poorly Defined Algorithms

Caillard S, Agodoa LY, Bohen EM, Abbott KC. Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: Characteristics, risk factors and prognosis. *Transplantation*. 2006; 81(6): 888-895.

Chandwani S, Wentworth C, Burke TA, Patterson TF. Utilization and dosage pattern of echinocandins for treatment of fungal infections in US hospital practice. *Curr Med Res Opin*. 2009; 25(2): 385-393.

Cuellar-Rodriguez J, Avery RK, Lard M, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. *Clin Infect Dis*. 2009; 49(5): 710-716.

Del Pozo JL, van de Beek D, Daly RC, Pulido JS, McGregor CG, Patel R. Incidence and clinical characteristics of ocular infections after heart transplantation: A retrospective cohort study. *Clin Transplant*. 2009; 23(4): 484-489.

Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients--an analysis of USRDS data. *Am J Transplant*. 2007; 7(3): 653-661.

Neff RT, Hurst FP, Falta EM, et al. Progressive multifocal leukoencephalopathy and use of mycophenolate mofetil after kidney transplantation. *Transplantation*. 2008; 86(10): 1474-1478.

Rogers MA, Langa KM, Kim C, et al. Contribution of infection to increased mortality in women after cardiac surgery. *Arch Intern Med*. 2006; 166(4): 437-443.

Sands KE, Yokoe DS, Hooper DC, et al. Detection of postoperative surgical-site infections: Comparison of health plan-based surveillance with hospital-based programs. *Infect Control Hosp Epidemiol*. 2003; 24(10): 741-743.

C. APPENDIX C: LIST AND DEFINITIONS OF ICD OR PROCEDURAL CODES INCLUDED IN ALGORITHMS

Because of the unusually broad nature of the outcome (infections), the 001-136 codes are listed in categories. Tables 3 and 4 provide more detailed descriptions of many codes.

Type of Code	Code	Description
General Code Categories for Infectious and Parasitic Diseases		
ICD-9-CM	001-009	Intestinal infectious diseases
ICD-9-CM	010-018	Tuberculosis
ICD-9-CM	020-027	Zoonotic bacterial diseases
ICD-9-CM	030-041	Other bacterial diseases
ICD-9-CM	042	Human immunodeficiency virus
ICD-9-CM	045-049	Poliomyelitis And Other Non-Arthropod-Borne Viral Diseases Of Central Nervous System
ICD-9-CM	050-059	Viral Diseases Accompanied By Exanthem
ICD-9-CM	060-066	Arthropod-Borne Viral Diseases
ICD-9-CM	070-079	Other Diseases Due To Viruses And Chlamydiae
ICD-9-CM	080-088	Rickettsioses And Other Arthropod-Borne Diseases
ICD-9-CM	909-099	Syphilis And Other Venereal Diseases
ICD-9-CM	100-104	Other Spirochetal Diseases
ICD-9-CM	110-118	Mycoses
ICD-9-CM	120-129	Helminthiases
ICD-9-CM	130-136	Other Infectious And Parasitic Diseases
ICD-9-CM	137-139	Late Effects Of Infectious And Parasitic Diseases
Codes to Identify Invasive Aspergillosis		
ICD-9	117.3	Aspergillosis
ICD-9	117.9	Other and Unspecified mycoses
ICD-9	348.8	Other conditions of the brain: cerebral calcification or fungus
ICD-9	484.6	Pneumonia with aspergillosis
ICD-9	484.7	Pneumonia in other systemic mycoses

ICD-9	495.4	Malt workers' lung alveolitis due to *Aspergillus clavatus*
Codes to Identify Urinary Tract / Kidney Infections		
ICD-9 and ICD-9-CM	590.x	Kidney infection, including pyelonephritis both acute and chronic (and others)
ICD-9 and ICD-9-CM	595.0	Acute cystitis
ICD-9 and ICD-9-CM	595.1	Urethral fistula
ICD-9 and ICD-9-CM	595.2	Urethral diverticulum
ICD-9 and ICD-9-CM	595.3	Urethral caruncle
ICD-9 and ICD-9-CM	595.4	Urethral false passage
ICD-9-CM	595.89	Other specified types of cystitis
ICD-9-CM	595.9	Cystitis unspecified
ICD-9-CM	597	Urethritis not sexually transmitted and urethral syndrome
ICD-9-CM	597.0	Urethral abscess
ICD-9-CM	597.8	Other urethritis
ICD-9-CM	597.80	Urethritis unspecified
ICD-9-CM	597.81	Urethral syndrome not otherwise specified
ICD-9-CM	597.89	Other urethritis
ICD-9 and ICD-9-CM	599.0	Urinary tract infection not otherwise specified
ICD-9-CM	599.x	Other disorders of the urethra and urinary tract (list seems too non-specific for infection)
ICD-9-CM	601.x	Inflammatory diseases of prostate
ICD-9-CM	604.x	Orchitis and epididymitis
ICD-9-CM	607.1	Balanoposthitis
ICD-9-CM	614.x	Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
ICD-9-CM	615.x	Inflammatory diseases of uterus except cervix
ICD-9-CM	616.0	Cervicitis and endocervicitis
ICD-9-CM	616.1	Vaginitis and vulvovaginitis
ICD-9-CM	616.3	Abcess of bartholin's gland
ICD-9-CM	616.4	Other abcess of vulva
ICD-9-CM	616.8x	Other specified inflammatory diseases of cervix vagina and vulva

Other Codes for Infections (Outside of 001-136 Infection Code Range and Not Urinary Tract)		
ICD-9-CM	254.1	Abcess of thymus
ICD-9-CM	320.x	Bacterial meningitis
ICD-9-CM	321.x	Meningitis due to other organisms
ICD-9-CM	322.x	Meningitis of unspecified cause
ICD-9-CM	323.x	Encephalitis myelitis and encephalomyelitis
ICD-9-CM	324.x	Intracranial and intraspinal abscess
ICD-9-CM	325.x	Phlebitis and thrombophlebitis of intracranial venous sinuses
ICD-9-CM	326.x	Late effects of intracranial abscess or pyogenic infection
ICD-9-CM	331.81	Reye's syndrome
ICD-9-CM	372.0x	Acute conjunctivitis
ICD-9-CM	372.1x	Chronic conjunctivitis
ICD-9-CM	372.2x	Blepharoconjunctivitis
ICD-9-CM	372.3x	Other and unspecified conjunctivitis
ICD-9	380.1	Infective otitis externa unspecified
ICD-9 and ICD-9-CM	382.0x	Acute suppurative otitis media
ICD-9-CM	382.1	Chronic tubotympanic suppurative otitis media
ICD-9-CM	382.2	Chronic atticoantral suppurative otitis media
ICD-9-CM	382.3	Unspecified chronic suppurative otitis media
ICD-9-CM	382.4	Unspecified suppurative otitis media
ICD-9-CM	383.0	Acute mastoiditis
ICD-9-CM	386.33	Suppurative labyrinthitis
ICD-9-CM	386.35	Viral labyrinthitis
ICD-9-CM	388.60	Otorrhea unspecified
ICD-9-CM	390	Rheumatic fever without heart involvement
ICD-9-CM	391.x	Rheumatic fever with heart involvement
ICD-9-CM	392.x	Rheumatic chorea
ICD-9-CM	393	Chronic rheumatic pericarditis
ICD-9	420.x	Acute pericarditis

ICD-9	421.x	Bacterial endocarditis
ICD-9-CM	421.x	Acute and subacute endocarditis
ICD-9-CM	422.x	Acute myocarditis
ICD-9	440.24	Athersclerosis of native arteries of the extremities with gangrene
ICD-9-CM	460.x	Acute nasopharyngitis
ICD-9-CM	461.x	Acute sinusitis
ICD-9-CM	462.x	Acute pharyngitis
ICD-9-CM	463.x	Acute tonsillitis
ICD-9-CM	464.x	Acute laryngitis and tracheitis
ICD-9-CM	465.x	Acute upper respiratory infections of multiple or unspecified sites
ICD-9-CM	466.x	Acute bronchitis and bronchiolitis
ICD-9-CM	472.x	Chronic pharyngitis and nasopharyngitis
ICD-9-CM	473.x	Chronic sinusitis
ICD-9-CM	474.0x	Chronic tonsillitis and adenoiditis
ICD-9-CM	475	Peritonsillar abscess
ICD-9-CM	476.x	Chronic laryngitis and laryngotracheitis
ICD-9-CM	477.x	Allergic rhinitis
ICD-9-CM	478.22	Parapharyngeal abscess
ICD-9-CM	478.24	Retropharyngeal abscess
ICD-9-CM	478.29	Other diseases of pharynx or nasopharynx
ICD-9-CM	480.x	Viral pneumonia
ICD-9-CM	481.x	Pneumococcal pneumonia (streptococcus pneumoniae pneumonia)
ICD-9-CM	482.x	Other bacterial pneumonia
ICD-9-CM	483.x	Pneumonia due to other specified organism
ICD-9-CM	484.x	Pneumonia in infectious diseases classified elsewhere
ICD-9-CM	485.x	Bronchopneumonia organism unspecified
ICD-9-CM	486.x	Pneumonia organism unspecified
ICD-9-CM	487.x	Influenza
ICD-9-CM	488.x	Influenza due to certain identified influenza viruses

ICD-9-CM	490.x	Bronchitis not specified as acute or chronic
ICD-9-CM	491.x	Chronic bronchitis
ICD-9-CM	494.x	Bronchiectasis
ICD-9-CM	510.x	Empyema
ICD-9-CM	511.x	Pleurisy
ICD-9-CM	513.x	Abscess of lung and mediastinum
ICD-9-CM	514.x	Pulmonary congestion and hypostasis
ICD-9-CM	515.x	Postinflammatory pulmonary fibrosis
ICD-9-CM	516.x	Other alveolar and parietoalveolar pneumonopathy
ICD-9-CM	517.x	Lung involvement in conditions classified elsewhere
ICD-9-CM	518.0	Pulmonary collapse
ICD-9-CM	518.1	Interstitial emphysema
ICD-9-CM	518.2	Compensatory emphysema
ICD-9-CM	518.3	Pulmonary eosinophilia
ICD-9-CM	518.4	Acute edema of lung unspecified
ICD-9-CM	518.5	Pulmonary insufficiency following trauma and surgery
ICD-9-CM	518.6	Allergic bronchopulmonary aspergilliosis
ICD-9	519.2	Mediastinitis
ICD-9-CM	522.5	Periapical abscess without sinus
ICD-9-CM	522.7	Periapical abscess with sinus
ICD-9-CM	527.3	Abscess of salivary gland
ICD-9	528.2	Oral aphthae (considered of unknown etiology, so unclear whether appropriate for infection)
ICD-9-CM	528.3	Cellulitis and abscess of oral soft tissues
ICD-9-CM	540.x	Acute appendicitis
ICD-9-CM	541.x	Appendicitis unqualified
ICD-9-CM	542.x	Other appendicitis
ICD-9	550.0x	Inguinal hernia with gangrene
ICD-9-CM	566.x	Abscess of anal and rectal regions

ICD-9-CM	567.x	Peritonitis and retroperitoneal infections
ICD-9-CM	569.5	Abscess of intestine
ICD-9-CM	572.0	Abscess of liver
ICD-9-CM	572.1	Portal pyemia
ICD-9-CM	572.2	Hepatic encephalopathy (seems too non-specific to classify as infection)
ICD-9-CM	573.1	Hepatitis in viral diseases classified elsewhere
ICD-9-CM	573.2	Hepatitis in other infectious diseases classified elsewhere
ICD-9-CM	573.3	Hepatitis unclassified
ICD-9-CM	575.0	Acute cholecystitis
ICD-9-CM	575.1x	Other cholecystitis
ICD-9-CM	611.0	Inflammatory disease of the breast
ICD-9-CM	670.x	Major puerperal infection, unspecified
ICD-9-CM	680.x	Carbuncle and furuncle
ICD-9-CM	681.x	Cellulitis and abscess of finger and toe
ICD-9-CM	682.x	Other cellulitis and abscess
ICD-9-CM	683.x	Acute lymphadenitis
ICD-9-CM	684.x	Impetigo
ICD-9-CM	685.x	Pilonidal cyst
ICD-9-CM	686.x	Other local infections of skin and subcutaneous tissue
ICD-9-CM	706.0	Acne varioliformis
ICD-9-CM	711.x	Arthropathy associated with infections
ICD-9	728.0	Infective myositis
ICD-9-CM	730.0x	Acute osteomyelitis
ICD-9-CM	730.1x	Chronic osteomyelitis
ICD-9-CM	730.2x	Unspecified osteomyelitis
ICD-9-CM	730.3x	Periostitis without mention of osteomyelitis
ICD-9-CM	730.8x	Other infections involving bone in diseases classified elsewhere
ICD-9-CM	730.9x	Unspecified infection of bone
ICD-9 and ICD-9-CM	790.7	Bacteremia

ICD-9-CM	790.8	Unspecified viremia
ICD-9-CM	996.62	Infection and inflammatory reaction due vascular device, implant and graft
ICD-9-CM	996.68	Infection and inflammatory reaction due to peritoneal dialysis catheter
ICD-9	996.6x	Infection and inflammatory reaction due to internal prosthetic device implant and graft
ICD-9-CM	997.62	Infection (chronic) of amputation stump
ICD-9-CM	998.5x	Postoperative infection not elsewhere classified
ICD-9-CM	999.3x	Other infection due to medical care not elsewhere classified
ICD-9-CM	V01.x	Contact with or exposure to communicable diseases (seems inappropriate to classify as infection)
ICD-9-CM	V02.x	Carrier or suspected carrier of infectious diseases
ICD-9-CM	V03.x	Need for prophylactic vaccination and inoculation against bacterial diseases (seems inappropriate to classify as infection)
ICD-9-CM	V04.x	Need for prophylactic vaccination and inoculation against viral diseases (seems inappropriate to classify as infection)
ICD-9-CM	V05.x	Need for other prophylactic vaccination and inoculation against single diseases (seems inappropriate to classify as infection)
ICD-9-CM	V06.x	Need for prophylactic vaccination and inoculation against combinations of diseases (seems inappropriate to classify as infection)
ICD-9	V08.x	Asymptomatic infection with HIV
ICD-9-CM	V09.x	Infection with drug-resistant microorganisms
Codes for Procedures or Conditions Not Specific to Infection		
DRG	103	Heart transplant or implant of heart assist system
DRG	302	Kidney transplant
DRG	480	Liver transplant and/or intestinal transplant
DRG	495	Lung transplant
ICD-9-CM procedure	36.1x	Coronary artery bypass graft surgery
Revenue code	38x	Purchased blood
Revenue code	39x	Donated blood
ICD-9-CM procedure	99.0x	Blood transfusion
ICD-9	394.x-397.x	Valvular heart disease

ICD-9	424.0x-424.1x	Valvular heart disease
ICD-9-CM	996.81	Complications of transplanted kidney
ICD-9-CM	996.82	Complications of transplanted liver
ICD-9-CM	996.83	Complications of transplanted heart
ICD-9-CM	996.84	Complications of transplanted lung
ICD-9-CM	996.85	Complications of transplanted bone marrow