1. Multidrug-resistant bacteria in solid organ transplant recipients

Clin Microbiol Infect 2014; 20 (Suppl. 7): 49–73

Cervera C., van Delden C., Gavald J., Welte T., Akova M., Carratal J. on behalf of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH)

ABSTRACT

Bacteria are the leading cause of infections after solid organ transplantation. In recent years, a progressive growth in the incidence of multidrug-resistant (MDR) and extensively-drug-reistant (XDR) strains has been observed. While methicillin-resistant *Staphylococcus aureus* (MRSA) infection is declining in non-transplant and SOT patients worldwide, vancomycin-resistant enterococci, MDR/XDR Enterobacteriaceae and MDR/XDR non-fermenters are progressively growing as a cause of infection in solid organ transplant (SOT) patients and represent a global threat. Some SOT patients develop recurrent infections, related to anatomical defects in many cases, which are difficult to treat and predispose patients to the acquisition of MDR pathogens. As the antibiotics active against MDR bacteria have several limitations for their use, which include less clinical experience, higher incidence of adverse effects and less knowledge of the pharmacokinetics of the drug, and, in most cases, are only available for parenteral administration, it is mandatory to know the main characteristics of these drugs to safely treat SOT patients with MDR bacterial infections. Nonetheless, preventive measures are the cornerstone of controlling the spread of these pathogens. Thus, applying the Center for Disease Control and Prevention's and the European Society of Clinical Microbiology and Infectious Diseases's recommended antibiotic policies and strategies to control the transmission of MDR strains in the hospital setting is essential for the management of SOT patients.

2. The characteristics and outcome of bacteraemia in renal transplant recipients and non-transplant renal patients

Infection (2016) 44:617–622

Melzer M., Santhakumaran T. and Welch C.

ABSTRACT

Background: There is lack of outcome data for bacteraemic patients on specialist renal units. We described demographic, clinical, microbiological data and outcomes for bacteraemic adult renal transplant and non-transplant patients at a London Teaching Hospital. We also assessed the appropriateness of empirical antibiotic policy.

Methods*:* From December 2012 to November 2013, demographic, clinical and microbiological data were collected on consecutive patients with bacteraemia on a specialist UK renal unit. Empirical anti-microbial policy, based upon sites of infection, was piperacillin/tazobactam and amikacin, or meropenem for graft pyelonephritis, and vancomycin and gentamicin for suspected central venous catheter (CVC) associated infection.

Results*:* 113 bacteraemic episodes occurred in 83 patients. One patient had two bacteraemic episodes, one on haemodialysis and another after transplantation so appear in both groups. In the non-transplant group, 30-day mortality was 4/59 (6.8 %), more than the renal transplant group, 0/25 (0 %). While graft pyelonephritis was the predominant cause of bacteraemic episodes in renal transplant patients, 25/36 (69.4 %), there were a variety of other causes in the non-transplant group including uncomplicated line associated bacteraemia, 36/77 (46.8 %), complicated line associated bacteraemia, 11/77 (14.3 %) and bacteraemia unrelated to vascular access sites 19/77 (24.7 %). Overall, commonest isolates were Methicillin-sensitive *Staphylococcus aureus* 20/77 (26.3 %), and *Escherichia coli* 28/113 (24.8 %). There were no Methicillin-resistant *Staphylococcus aureus* isolates and, among Enterobacteriaceae, 15/57 (26.3 %) were extended spectrum beta-lactamase producers.

Conclusions*:* Death only occurred in the non-transplant renal group. Empirical antibiotic treatment with either piperacillin/tazobactam and amikacin, or meropenem was appropriate for renal transplant recipients as most bacteraemic episodes were secondary to graft pyelonephritis. Vancomycin and gentamicin was appropriate empirical antibiotic treatment for non-transplant patients with CVC associated infections, but not optimal for other sites of infection.

3. Colonisation with methicillin-resistant Staphylococcus aureus prior to renal transplantation is associated with long-term renal allograft failure

Transplant International 27 (2014) 926–930

Moore C., Davis N. F., Burke J. P., Power R., Mohan P., Hickey D., Smyth G., Eng M. and Little D. M.

Summary

Renal transplant recipients are at an increased risk of develo*ping Methicillinresistant Staphylococcus aureus* due to their immunosuppressed status. Herein, we investigate the incidence of MRSA infection in patients undergoing renal transplantation and determine the effect of MRSA colonisation on renal allograft function and overall mortality. Between January 1st 2007 and December 31st 2012, 1499 consecutive kidney transplants performed in our transplant unit and a retrospective 1:2 matched case-control study was performed on this patient cohort. The 1-, 3- and 5-year overall graft survival rates were 100%, 86% and 78%, respectively, in MRSA positive recipients compared with 100%, 100% and 93%, respectively, in the control group ($P < 0.05$). The 1-, 3- and 5-year overall patient survival rates were 100%, 97% and 79%, respectively, in MRSA positive recipients compared with 100%, 100% and 95%, respectively, in the control group ($P = 0.1$). In a multiple logistic regression analysis, colonization with MRSA pre-operatively was an independent predictor for renal allograft failure at 5 years (hazard ratio: 4.6, 95% confidence interval: 1–30.7, $P = 0.048$). These findings demonstrate that the incidence of long-term renal allograft failure is significantly greater in this patient cohort compared with a matched control population.

4. Epidemiology and outcomes of carbapenemresistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients

Transpl Infect Dis 2015: 17: 800–809.

Pouch S.M., Kubin C.J., Satlin M.J., Tsapepas D.S., Lee J.R., Dube G., Pereira M.R..

ABSTRACT

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria is a frequently encountered clinical condition, but its clinical impact is unknown. We conducted a retrospective cohort study to define the epidemiology and outcomes for patients with CRKP bacteriuria. Patients with positive urine cultures for CRKP were classified as having asymptomatic bacteriuria (ASB) or symptomatic urinary tract infection (UTI). Among 105 patients with CRKP bacteriuria, 80% (84/105 patients) and 20% (21/105 patients) had ASB and UTI, respectively. Older age (*P*_0.002) and higher Charlson's comorbidity index scores (*P* = 0.001) were associated with ASB. The median duration of hospitalization prior to CRKP bacteriuria was significantly longer for patients with ASB versus UTI (8.5 versus 2 days; *P* = 0.05). In multivariate analysis, male sex (odds ratio [OR], 4.69 [95% confidence interval (CI), 1.44 to 15.26]; *P*_0.01), solid-organ transplantation (OR, 4.50 [95% CI, 1.39 to 14.52]; *P* = 0.01), and neurogenic bladder (OR, 18.62 [95% CI, 1.75 to 197.52]; *P* = 0.01) were independently associated with UTI. Ten percent (8/84) of the patients with ASB received antimicrobial therapy. The treatment success rate for patients with UTIs was 90% (19/21 patients), including all patients who received doxycycline (*n* = 9). The overall 30-day mortality rate was 6% (6/105 patients); the deaths were unrelated to CRKP infections. Secondary CRKP infections, including UTIs, were notably absent among patients with ASB who were followed for 90 days. In conclusion, identification of CRKP in the urine was most commonly associated with ASB and did not lead to subsequent infections or death among asymptomatic patients. Factors associated with UTIs included male sex, solid-organ transplantation, and neurogenic bladder. Doxycycline may be an effective therapy for CRKP UTIs.

5. Epidemiology and Outcomes of Multiple Antibiotic–Resistant Bacterial Infection in Renal Transplantation

Transplantation Proceedings, 39, 2222–2224 (2007)

Linares L., Cervera C., Cofán F., Ricart M.J., Esforzado N., Torregrosa V., Oppenheimer F., Campistol J.M., Marco F. and Moreno A.

ABSTRACT

Background. Mutiresistant bacterial infections are an emerging problem in the nosocomial setting. Our objectives were to describe the incidence, outcome, and risk factors for acquisition of multiresistant bacteria among renal transplant recipients.

Methods. We prospectively followed patients undergoing kidney transplantation over a 3-year period. We collected demographic features, underlying chronic diseases, and main transplant characteristics and complications. Multiple antibiotic resistance was defined for the most important bacteria: Enteric gram-negative bacilli resistant to betalactamics, cephalosporins, and quinolones; *Staphylococcus aureus* resistant to methicillin, cotrimoxazole, and clindamcin; *Enterococcus* spp resistant to ampicillin and quinolones; nonfermentator bacilli resistant to all antibiotics except aminoglycosides and collistin.

Results. Overall, 416 patients included 65 double transplants (62 kidney-pancreas and three kidney-liver) of mean age 48.5 years, and 57% men. Infection with multiresistant bacteria was observed in 58 patients (14%). Most frequent multiresistant bacteria were: *Escherichia coli* (*n* = 33), *Klebsiella* spp (*n* = 15), *Citrobacter* spp (*n* = 8), *Enterobacter* spp (*n* = 5), *Morganella morganii* (*n* = 2), *Pseudomonas aeruginosa* (*n* = 16), *Acinetobacter baumanii* (*n* = 2), *Enterococcus* spp (*n* = 9) and methicillin-resistant *S. aureus* (MRSA, *n* = 2). Age greater than 50 years, hepatitis C virus infection, double kidney-pancreas transplantation, requirement for posttransplant hemodialysis, surgical reoperation, and requirement for nephrostomy were independent variables associated with multiresistant bacterial infection. Most used antibiotics for treatment were: carbapenems (65%), amikacin (12%), linezolid, piperacillin-tazobactam, vancomycin, collistin, and fosfomycin. Infection with multiresistant bacteria was associated with a worse prognosis (graft loss or death, 19% vs 8%, *P* = .009).

Conclusions. The incidence of infection with multiresistant bacteria in our renal transplant cohort was high, being most frequently cephalosporin-resistant enteric gramnegative bacilli and multiresistant *P aeruginosa.* Methicillin-resistant *S. aureus* incidence was low. Infection with multiresistant bacteria conferred a worse prognosis.

6. Carbapenemresistant Klebsiella pneumoniae infections in kidney transplant recipients: a case-control study.

Transpl Infect Dis 2014: 16: 775–782.

Simkins J., Muggia V., Cohen H.W. ,Minamoto G.Y.

ABSTRACT

Introduction. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections have emerged as a significant challenge in solid organ transplantation. CRKP infections in other patient populations have been associated with higher mortality, when compared to infections caused by carbapenem-sensitive *K. pneumoniae* (CSKP).

Aims. The aim of this study was to evaluate possible risk factors, clinical characteristics, and outcomes of CRKP infections compared with CSKP infections in kidney transplant recipients (KTR).

Methods. We retrospectively investigated 13 CRKP infections and 39 CSKP infections in KTR (2006–2010).

Results. CRKP was not significantly associated with age, gender, or comorbidities. CRKP infections were significantly associated with recent exposure to broad-spectrum antibiotics and were more likely to have been managed on an inpatient basis and to have required source control. CRKP was significantly associated with earlier mortality. Six of 13 (46%) patients with CRKP infection, and none of the patients with CSKP infection, died within 6.5 months of infection onset. Although cases and controls did not differ significantly with respect to diabetes, all patients (100%, n = 9) who died during the study had diabetes, while 58% of the 43 survivors had diabetes (P = 0.02).

Conclusion. In conclusion, CRKP compared with CSKP is associated with greater risk of mortality. Investigations on ways to better prevent CRKP are urgently needed.

7. Risk Factors and Outcomes of Bacteremia Caused by Drug-Resistant ESKAPE Pathogens in Solid-Organ Transplant Recipients

Transplantation 2013;96: 843-849

Bodro M., Sabé N., Tubau F., Lladó L., Baliellas C., Roca J., Cruzado J. M., and Carratala J.

Background. Although infections due to the six ESKAPE pathogens have recently been identified as a serious emerging problem, information regarding bacteremia caused by these organisms in solid-organ transplant (SOT) recipients is lacking. We sought to determine the frequency, risk factors, and outcomes of bacteremia due to drugresistant ESKAPE (rESKAPE) organisms in liver, kidney, and heart adult transplant recipients.
Methods. All episodes of bacteremia prospectively documented in hospitalized SOT recipients from 2007 to 2012 were analyzed.
Results. Of 276 episodes of bacteremia, 54 (19.6%) were due to rESKAPE strains (vancomycin-resistant *Enterococcus faecium* [0], methicillin-resistant *Staphylococcus aureus* [5], extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* [10], carbapenem-resistant *Acinetobacter baumannii* [8], carbapenem- and quinolone-resistant *Pseudomonas aeruginosa* [26], and derepressed chromosomal β-lactam and extended-spectrum β-lactamase-producing *Enterobacter* species [5]). Factors independently associated with rESKAPE bacteremia were prior transplantation, septic shock, and prior antibiotic therapy. Patients with rESKAPE bacteremia more often received inappropriate empirical antibiotic therapy than the others (41% vs. 21.6%; P=0.01). Overall case-fatality rate (30 days) was higher in patients with rESKAPE bacteremia (35.2% vs. 14.4%; P=0.001).
Conclusions. Bacteremia due to rESKAPE pathogens is frequent in SOT recipients and causes significant morbidity and mortality. rESKAPE organisms should be considered when selecting empirical antibiotic therapy for hospitalized SOT recipients presenting with septic shock, Particularly those with prior transplantation and antibiotic use.

8. Amikacin Prophylaxis and Risk Factors for Surgical Site Infection After Kidney Transplantation
Transplantation 2015;99: 521–527
Freire M. P., Antonopoulos I. M., Piovesan A. C., Moura M. L., de Paula F. J., Spadao F., Guimaraes T., David-Neto E., Nahas W. C. and Pierrotti L. C..

Background. Antibiotic prophylaxis plays a major role in preventing surgical site infections (SSIs). This study aimed to evaluate antibiotic prophylaxis in kidney transplantation and identify risk factors for SSIs.
Methods. We evaluated all kidney transplantation recipients from January 2009 and December 2012.We excluded patients who died within the first 72 hr after transplantation, were undergoing simultaneous transplantation of another organ, or were below 12 years of age. The main outcome measure was SSI during the first 60 days after transplantation.
Results. A total of 819 kidney transplants recipients were evaluated, 65% of whom received a deceased-donor kidney. The antibiotics used as prophylaxis included cephalosporin, in 576 (70%) cases, and amikacin, in 233 (28%).We identified SSIs in 106 cases (13%), the causative agent being identified in 72 (68%). Among the isolated bacteria, infections caused by extended-spectrum β-lactamase–producing Enterobacteriaceae predominated. Multivariate analysis revealed that the risk factors for post-kidney transplantation SSIs were deceased donor, thin ureters at kidney transplantation, antithymocyte globulin induction therapy, blood transfusion at the transplantation procedure, high bodymass index, and diabetes mellitus. The only factor associated with a reduction in the incidence of SSIs was amikacin use as antibiotic prophylaxis. Factors associated with reduced graft survival were: intraoperative blood transfusions, reoperation, human leukocyte antigen mismatch, use of nonstandard immunosuppression therapy, deceased donor, post-kidney transplantation SSIs, and delayed graft function.
Conclusion. Amikacin prophylaxis is a useful strategy for preventing SSIs.

9. Impact of Antibiotic Resistance on the Development of Recurrent and Relapsing Symptomatic Urinary Tract Infection in Kidney Recipients

American Journal of Transplantation 2015; 15: 1021–1027

Bodro M., Sanclemente G., Lipperheide I., Allali M., Marco F., Bosch J., Cofan F., Ricart M. J., Esforzado N., Oppenheimer F., Moreno A. and Cervera C.

ABSTRACT

We sought to determine the frequency, risk factors, and clinical impact of recurrent urinary tract infections (UTI) in kidney transplant recipients. Of 867 patients who received a kidney transplant between 2003 and 2010, 174 (20%) presented at least one episode of UTI. Fifty-five patients presented a recurrent UTI (32%) and78%of them could be also considered relapsing episodes. Recurrent UTI was caused by extended-spectrum betalactamase (ESBL)–producing *Klebsiella pneumoniae* (31%), followed by non-ESBL producing *Escherichia coli* (15%), multidrug-resistant (MDR) *Pseudomonas aeruginosa* (14%), and ESBL-producing *E. coli* (13%). The variables associated with a higher risk of recurrent UTIwere a first or second episode of infection by MDR bacteria (OR 12; 95%CI 528), age >60 years (OR 2.2; 95%CI 1.15.1), and reoperation (OR 3; 95%CI 1.37.1). In addition, more relapses were recorded in patients with UTI caused by MDR organisms than in those with susceptible microorganisms. There were no differences in acute rejection, graft function, graft loss or 1 year mortality between groups. In conclusion, recurrent UTI is frequent among kidney recipients and associated with MDR organism. Classic risk factors for UTI (female gender and diabetes) are absent in kidney recipients, thus highlighting the relevance of uropathogens in this population.

10. A retrospective study to describe the epidemiology and outcomes of opportunistic infections after abdominal organ transplantation

Transpl Infect Dis. 2017;e12691.

Helfrich M., Dorschner P., Thomas K., Stosor V. and Ison M. G.

ABSTRACT

Background: Most epidemiologic studies of opportunistic infections (OI) following abdominal organ transplantation are derived prior to the era of contemporary immunosuppression and prophylaxis. These studies suggest that most OI occur within the first 6 months post transplant.

Method: In this single-center, retrospective cohort study, we describe the epidemiology of OI in 359 consecutive abdominal organ transplant recipients, in the era of contemporary prophylaxis practices and alemtuzumab induction in kidney and simultaneous pancreas-kidney transplant recipients.

Results: Ninety patients (25.1%) developed OI, with 53.3% of these occurring beyond 6 months. The most common OI were BK polyomavirus nephropathy (5.0%), cytomegalovirus (10.2%), varicella zoster virus (4.4%), and herpes simplex virus (1.1%), which typically occurred after discontinuation of antiviral prophylaxis, and *Clostridium difficile* infections (7.8%).

Conclusion: OI had no impact on patient or graft survival at 12 months post transplant. In the era of contemporary immunosuppression and prophylaxis, a significant proportion of OI occur beyond 6 months. Additional strategies may be important to reduce the incidence of such late-onset infections.

11. Risk Factors for Infection with Extended-Spectrum and AmpC b-Lactamase-Producing Gram-Negative Rods in Renal Transplantation

American Journal of Transplantation 2008; 8: 1000–1005

Linares L., Cervera C., Cofán F., Lizaso D., Marco F., Ricart M. J., Esforzado N., Oppenheimer F., Campistol J. M. and Moreno A.

ABSTRACT

Increasing prevalence of infections caused by multiresistant gram-negative enteric bacilli due to synthesis of extended-spectrum β-lactamase (ESBL) or to desrepressed chromosomic AmpC β-lactamase (AmpC) is a major concern in the hospitalized patient population.

Renal transplant recipients are especially susceptible to these infections. A cohort observational study in a 3-year period was performed. ESBL-production was determined by phenotypic analysis based on the CLSI recommendations. A multi-variate logistic regression analysis was performed to identify independent variables associated with multi-resistant gram-negative bacilli infection. The study included 417 patients (61 double kidney-pancreas recipients). The incidence of ESBL-producing and desrepressed chromosomic AmpC β-lactamase resistance was 11.8% (49 patients). The most frequent bacteria isolated was E. coli (35/60 isolations), followed by *Klebsiella* spp (12/60 isolations). Double kidney-pancreas transplantation (OR 3.5, CI95% 1.6–7.8), previous use of antibiotics (OR 2.1,CI95% 1.1–4.1), posttransplant dialysis requirement (OR 3.1, CI95% 1.5–6.4) and posttransplant urinary obstruction (OR 5.8, CI95% 2.2–14.9) were independent variables associated with these multiresistant gram-negative enteric bacilli infections. The incidence of ESBL-producing and desrepressed AmpC β-lactamase gram-negative enteric bacilli infection in our population was high. These infections are associated with significant morbidity after renal transplantation.

12. Urinary Tract Infections in Kidney Transplant Patients Due to Escherichia coli and Klebsiella pneumoniae-Producing Extended-Spectrum β-Lactamases: Risk Factors and Molecular Epidemiology

PLoS ONE 10(8)

Espinar M. J., Miranda I. M., Costa de Oliveira S., Rocha R., Rodrigues A. G., Pina-Vaz C.

ABSTRACT

Urinary tract infection (UTI) is a common complication after kidney transplantation, often associated to graft loss and increased healthcare costs. Kidney transplant patients (KTPs) are particularly susceptible to infection by *Enterobacteriaceae*-producing extended-spectrum β-lactamases (ESBLs). A retrospective case-control study was conducted to identify independent risk factors for ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in non-hospitalized KTPs with UTI. Forty-nine patients suffering from UTI by ESBL-producing bacteria (ESBL-P) as case group and the same number of patients with UTI by ESBL negative (ESBL-N) as control-group were compared. Clinical data, renal function parameters during UTI episodes, UTI recurrence and relapsing rate, as well as risk factors for recurrence, molecular characterization of isolates and the respective antimicrobial susceptibility profile were evaluated. Diabetes mellitus ($p < 0.007$), previous antibiotic prophylaxis ($p=0.017$) or therapy ($p<0.001$), previous UTI ($p=0.01$), relapsing infection ($p=0.019$) and patients with delayed graft function after transplant ($p=0.001$) represented risk factors for infection by ESBL positive *Enterobacteriaceae* in KTPs. Interestingly, the period of time between data of transplantation and data of UTI was shorter in case of ESBL-P case-group (28.8 months) compared with ESBL-N control-group (50.9 months). ESBL-producing bacteria exhibited higher resistance to fluoroquinolones ($p=0.002$), trimethoprim-sulfamethoxazole ($p<0.001$) and gentamicin ($p<0.001$). Molecular analysis showed that bla_{CTX-M} was the most common ESBL encoding gene (65.3%), although in 55.1% of the cases more than one ESBL gene was found. In 29.4% of *K. pneumoniae* isolates, three *bla*-genes (bla_{CTX-M}- bla_{TEM}-bla_{SHV}) were simultaneously detected. Low estimated glomerular filtration rate ($p=0.009$) was found to be risk factor for UTI recurrence. Over 60% of recurrent UTI episodes were caused by genetically similar strains. UTI by ESBL-producing *Enterobacteriaceae* in KTPs represent an important clinical challenge regarding not only hospitalized patients but also concerning outpatients.

13. Bacterial urinary tract infection after solid organ transplantation in the RESITRA cohort.
Transpl Infect Dis 2012: 14: 595–603.
Vidal E., Torre-Cisneros J., Blanes M., Montejo M., Cervera C., Aguado J.M., Len O., Carratalá J., Cordero E., Bou G., Muñoz P., Ramos A., Gurguí M., Borrell N., Fortún J., on behalf of the Spanish Network for Research in Infectious Diseases (REIPI).

ABSTRACT
Background. Urinary tract infection (UTI) is the most common infection in renal transplant patients, but it is necessary to determine the risk factors for bacterial UTI in recipients of other solid organ transplants (SOTs), as well as changes in etiology, clinical presentation, and prognosis.
Methods. In total, 4388 SOT recipients were monitored in 16 transplant centers belonging to the Spanish Network for Research on Infection in Transplantation (RESITRA). The frequency and characteristics of bacterial UTI in transplant patients were obtained prospectively from the cohort (September 2003 to February 2005).
Results. A total of 192 patients (4.4%) presented 249 episodes of bacterial UTI (0.23 episodes per 1000 transplantation days); 156 patients were kidney or kidney–pancreas transplant recipients, and 36 patients were liver, heart, and lung transplant recipients. The highest frequency was observed in renal transplants (7.3%). High frequency of cystitis versus pyelonephritis without related mortality was observed in both groups. The most frequent etiology was *Escherichia coli* (57.8%), with 25.7% producing extended-spectrum β-lactamase (ESBL). In all transplants but renal, most cases occurred in the first month after transplantation. Cases were uniformly distributed during the first 6 months after transplantation in renal recipients. Age (odds ratio [OR] per decade 1.1, 95% confidence interval [CI] 1.02–1.17), female gender (OR 1.74, 95% CI 1.42–2.13), and the need for immediate posttransplant dialysis (OR 1.63, 95% CI 1.29–2.05) were independent variables associated with bacterial UTI in renal and kidney– pancreas recipients. The independent risk factors identified in non-renal transplants were age (OR per decade 1.79, 95% CI 1.09–3.48), female gender (OR 1.7, 95% CI 1.43–2.49), and diabetes (OR 1.02, 95% CI 1.001–1.040).
Conclusions. UTI was frequent in renal transplants, but also not unusual in non-renal transplants. Because *E. coli* continues to be the most frequent etiology, the emergence of ESBL-producing strains has been identified as a new problem. In both populations, most cases were cystitis without related mortality. Although the first month after transplantation was a risk period in all transplants, cases were uniformly distributed during the first 6 months in renal transplants. Age and female gender were identified as risk factors for UTI in both populations. Other particular risk factors were the need for immediate post-transplant dialysis in renal transplants and diabetes in non-renal transplants.

14. Losing ground: multidrug-resistant bacteria in solid-organ transplantation

Curr Opin Infect Dis 2012, 25:445–449

Herati R. S. and Blumberg E. A.

Purpose of review

Multidrug-resistant (MDR) bacteria can cause serious infections in solid-organ transplant recipients. This review focuses on the role of MDR bacteria in posttransplant infections.

Recent findings

The incidence of MDR bacterial infections among solid-organ transplant recipients is increasing steadily. There is wide variability in the specific MDR bacteria causing infection based on the organ transplanted, geography, timing with respect to transplantation, and additional risk factors. Rarely these infections can be transmitted via the transplanted organ. Prompt recognition and early appropriate treatment of MDR bacterial infections are especially critical in this immunosuppressed population. In order to promptly initiate appropriate antimicrobial therapy for these organisms, high-risk patients should receive appropriate broad-spectrum antibiotics.

Summary

MDR bacterial infections vary widely and require careful antibiotic selection to reduce mortality.

15. Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

BMC Infectious Diseases 2014, 14:177

Shenoy E. S., Paras M. L., Noubary F., Walensky R. P. and Hooper D. C.

ABSTRACT

Background: No published systematic reviews have assessed the natural history of colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE). Time to clearance of colonization has important implications for patient care and infection control policy.

Methods: We performed parallel searches in OVID Medline for studies that reported the time to documented clearance of MRSA and VRE colonization in the absence of treatment, published between January 1990 and July 2012.

Results: For MRSA, we screened 982 articles, identified 16 eligible studies (13 observational studies and 3 randomized controlled trials), for a total of 1,804 non-duplicated subjects. For VRE, we screened 284 articles, identified 13 eligible studies (12 observational studies and 1 randomized controlled trial), for a total of 1,936 non-duplicated subjects. Studies reported varying definitions of clearance of colonization; no study reported time of initial colonization. Studies varied in the frequency of sampling, assays used for sampling, and follow-up period. The median duration of total follow-up was 38 weeks for MRSA and 25 weeks for VRE. Based on pooled analyses, the model-estimated median time to clearance was 88 weeks after documented colonization for MRSA-colonized patients and 26 weeks for VRE-colonized patients. In a secondary analysis, clearance rates for MRSA and VRE were compared by restricting the duration of follow-up for the MRSA studies to the maximum observed time point for VRE studies (43 weeks). With this restriction, the model-fitted median time to documented clearance for MRSA would occur at 41 weeks after documented colonization, demonstrating the sensitivity of the pooled estimate to length of study follow-up.

Conclusions: Few available studies report the natural history of MRSA and VRE colonization. Lack of a consistent definition of clearance, uncertainty regarding the time of initial colonization, variation in frequency of sampling for persistent colonization, assays employed and variation in duration of follow-up are limitations of the existing published literature. The heterogeneity of study characteristics limits interpretation of pooled estimates of time to clearance, however, studies included in this review suggest an increase in documented clearance over time, a result which is sensitive to duration of follow-up.

16. MRSA and VRE Colonization in Solid Organ Transplantation: A Meta-Analysis of Published Studies

American Journal of Transplantation 2014; 14: 1887–1894

Ziakas P. D., Pliakos E. E., Zervou F. N., Knoll B. M., Rice L. B. and Mylonakis E.

ABSTRACT

The burden of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) colonization among the increasing number of solid organ transplant patients has not been systematically explored. We searched PubMed and EMBASE for pertinent articles, performed a metaanalysis of prevalence across eligible studies and estimated the risk of ensuing MRSA or VRE infections relative to colonization status. We stratified effects in the pretransplant and posttransplant period. Twentythree studies were considered eligible. Seventeen out of 23 (74%) referred to liver transplants. Before transplantation, the pooled prevalence estimate for MRSA and VRE was 8.5% (95% confidence interval [CI] 3.2–15.8) and 11.9% (95% CI 6.8–18.2), respectively. MRSA estimate was influenced by small studies and was lower (4.0%; 95% CI 0.4–10.2) across large studies (>200 patients). After transplantation, the prevalence estimates were 9.4% (95% CI 3.0–18.5) for MRSA and 16.2% (95% CI 10.7–22.6) for VRE. Pretransplant as well as posttransplant MRSA colonization significantly increased the risk for MRSA infections (pooled risk ratio [RR] 5.51; 95% CI 2.36–12.90 and RR 10.56; 95% CI 5.58–19.95, respectively). Pretransplant and posttransplant VRE colonization were also associated with significant risk of VRE infection (RR 6.65; 95% CI 2.54–17.41 and RR 7.93; 95% CI 2.36–26.67, respectively). Solid organ transplantation is a high-risk setting for MRSA and VRE colonization, and carrier state is associated with infection. Upgraded focus in prevention and eradication strategies is warranted.

17. Methicillin-Resistant, Vancomycin-Intermediate and Vancomycin-Resistant Staphylococcus aureus Infections in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 50–58

Garzoni C., Vergidis P. and the AST Infectious Diseases Community of Practice

Abstract not available

18. Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial

American Journal of Transplantation 2016; 16: 2943–2953

Origuen J., López-Medrano F., Fernández-Ruiz M., Polanco N., Gutiérrez E., González E., Mérida E., Ruiz-Merlo T., Morales-Cartagena A., Pérez-Jacoiste Asín M. A., García-Reyne A., San Juan R., Orellana M. A., Andrés A. and Aguado J. M.

ABSTRACT

The indication for antimicrobial treatment of asymptomatic bacteriuria (AB) after kidney transplantation (KT) remains controversial. Between January 2011 and December 2013, 112 KT recipients that developed one episode or more of AB beyond the second month after transplantation were included in this open-label trial. Participants were randomized (1:1 ratio) to the treatment group (systematic antimicrobial therapy for all episodes of AB occurring ≤24 mo after transplantation [53 patients]) or control group (no antimicrobial therapy [59 patients]). Systematic screening for AB was performed similarly in both groups. The primary outcome was the occurrence of acute pyelonephritis at 24-mo follow-up. Secondary outcomes included lower urinary tract infection, acute rejection, *Clostridium difficile* infection, colonization or infection by multidrug-resistant bacteria, graft function and allcause mortality. There were no differences in the primary outcome in the intention-to-treat population (7.5% [4 of 53] in the treatment group vs. 8.4% [5 of 59] in the control group; odds ratio [OR] 0.88, 95% confidence interval [CI] 0.22–3.47) or the per-protocol population (3.8% [1 of 26] in the treatment group vs. 8.0% [4 of 50] in the control group; OR 0.46, 95% CI 0.05–4.34). Moreover, we found no differences in any of the secondary outcomes. In conclusion, systematic screening and treatment of AB beyond the second month after transplantation provided no apparent benefit among KT recipients (NCT02373085).

19. Clostridium difficile infection among kidney transplant recipients: frequency, clinical presentation, and outcome

APMIS 2014, 123: 234–239

Lionaki S., Panagiotellis K., Moris D., Daikos G., Psyhogiou M., Vernadakis S., Zavos G. and Boletis J.

ABSTRACT

The objective of this study was to evaluate the frequency of Clostridium Difficile Infection (CDI) among kidney transplant recipients and describe the clinical picture in correlation with the presence of certain risk factors. We included kidney transplant recipients with a functioning graft, who were admitted during the period 1/2012-12/2013, and patients with ESRD who were admitted to undergo Kidney Transplantation (KTx) from a deceased or a living donor in the same period. Patients were screened following clinical indication of gastrointestinal infection. CDI diagnosis was based on a positive stool sample for CD toxins and stool culture. Within the period 2012-2013, we recorded 24 cases of CDI in 19 patients, accounting for a frequency of 5.4% of CDI in our population. In addition to diarrhea, 63.15% of the patients presented with fever, 31.25% with anorexia, while abdominal pain was a rare symptom (0.53%). None of the patients had ileus, bowel obstruction or megacolon. Fourteen patients (73.7%) had a history of recent exposure (15 days) to antimicrobial agents prior to the evolution of CDI symptoms. A relapse of the CDI infection was identified in five cases. CDI infection is a significant factor of morbidity in patients with KTx and should be considered in the clinical setting of diarrhea, even in cases with no exposure to antibiotic agents.

20. Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection
PLoS ONE 11(2): e0149521.
Lapointe-Shaw L., Tran K. L., Coyte P. C., Hancock-Howard R. L., Powis J., Poutanen S. M. and Hota S.

ABSTRACT
Objective: To assess the cost-effectiveness of six treatment strategies for patients diagnosed with recurrent *Clostridium difficile* infection (CDI) in Canada: 1. oral metronidazole; 2. oral vancomycin; 3.oral fidaxomicin; 4. fecal transplantation by enema; 5. fecal transplantation by nasogastric tube; and 6. fecal transplantation by colonoscopy.
Perspective: Public insurer for all hospital and physician services.
Setting: Ontario, Canada.
Methods: A decision analytic model was used to model costs and lifetime health effects of each strategy for a typical patient experiencing up to three recurrences, over 18 weeks. Recurrence data and utilities were obtained from published sources. Cost data was obtained from published sources and hospitals in Toronto, Canada. The willingness-to-pay threshold was $50,000/QALY gained.
Results: Fecal transplantation by colonoscopy dominated all other strategies in the base case, as it was less costly and more effective than all alternatives. After accounting for uncertainty in all model parameters, there was an 87% probability that fecal transplantation by colonoscopy was the most beneficial strategy. If colonoscopy was not available, fecal transplantation by enema was cost-effective at $1,708 per QALY gained, compared to metronidazole.
In addition, fecal transplantation by enema was the preferred strategy if the probability of recurrence following this strategy was below 8.7%. If fecal transplantation by any means was unavailable, fidaxomicin was cost-effective at an additional cost of $25,968 per QALY gained, compared to metronidazole.
Conclusion
Fecal transplantation by colonoscopy (or enema, if colonoscopy is unavailable) is cost-effective for treating recurrent CDI in Canada. Where fecal transplantation is not available, fidaxomicin is also cost-effective.

21. Novel therapeutic strategies for Clostridium difficile infections

Expert Opin. Ther. Targets (2016) 20(3):269-285

Ünal C. M. and Steinert M.

ABSTRACT

Introduction: In recent years, *Clostridium difficile* has become the primary cause of antibiotic-associated diarrhea and pseudomembranous colitis, resulting in long and complicated hospital stays that represent a serious burden for patients as well as health care systems. Currently, conservative treatment of *C. difficile* infection (CDI) relies on the antibiotics vancomycin, metronidazole or fidaxomicin, or in case of multiple recurrences, fecal microbiota transplantation (FMT).

Areas covered: The fast-spreading, epidemic nature of this pathogen urgently necessitates the search for alternative treatment strategies as well as antibiotic targets. Accordingly, in this review, we highlight the recent findings regarding virulence associated traits of *C. difficile*, evaluate their potential as alternative drug targets, and present current efforts in designing inhibitory compounds, with the aim of pointing out possibilities for future treatment strategies.

Expert opinion: Increased attention on systematic analysis of the virulence mechanisms of *C. difficile* has already led to the identification of several alternative drug targets. In the future, applying state of the art 'omics' and the development of novel infection models that mimic the human gut, a highly complex ecological niche, will unveil the genomic and metabolic plasticity of this pathogen and will certainly help dealing with future challenges.

22. Fidaxomicin: The Newest Addition to the Armamentarium Against Clostridium difficile Infections

Clinical Therapeutics/Volume 34, Number 1, 2012

Lancaster J. W. and Matthews S. James

ABSTRACT

Background: Fidaxomicin, a macrolide antibiotic, was the first medication for the management of *Clostridium difficile* infections (CDI) to be approved by the US Food and Drug Administration in more than 20 years.

Objective: This article reviews published literature on fidaxomicin for management of CDI, including its chemistry, spectrum of activity, pharmacokinetic properties, pharmacodynamics, therapeutic efficacy, adverse events, dosing, administration, and pharmacoeconomic considerations.

Methods: Pertinent English-language literature was reviewed through searches of MEDLINE, EMBASE, and BIOSIS from 1975 through September 2011. Reference lists of identified publications and published abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy meetings were also reviewed. Search terms included, but were not limited to, *fidaxomicin*, *difimicin*, *lipiarmycin*, *tiacumicin B*, *OPT-80*, *Clostridium spp*, and *diarrhea*.

Results: A total of 79 publications were identified and 10 were excluded; 6 review articles and 4 abstracts that were later published as articles. Fidaxomicin's in vitro profile is favorable compared with oral metronidazole and vancomycin, with minimum inhibitory concentrations against *C difficile* that are 2 dilutions lower. From the 2 published Phase III trials, fidaxomicin was deemed to be noninferior in the treatment of mild to moderate CDI compared with oral vancomycin. Recurrence rates for all strains of CDI were lower with fidaxomicin than vancomycin. Adverse events associated with fidaxomicin were similar to placebo, with nausea and vomiting being the most common. Although no pharmacoeconomic studies have compared fidaxomicin with metronidazole or vancomycin, the current price exceeds $2500 (US) per treatment course.

Conclusions: Reports suggest that fidaxomicin is noninferior to oral vancomycin in the treatment of mild or moderate CDI, although no published comparisons with metronidazole exist to date. Additionally, fidaxomicin improved outcomes compared with oral vancomycin in terms of rates of relapse and recurrent CDI, and in patients who might require concomitant antibiotics. Prospective, randomized studies comparing fidaxomicin with metronidazole in the treatment of mild or moderate CDI, as well as against vancomycin for severe CDI, should be undertaken to clarify the exact role of fidaxomicin in clinical practice.

23. Prevalence of Clostridium difficile Infection among Solid Organ Transplant Recipients: A Meta-Analysis of Published Studies.

PLoS ONE 10(4): e0124483

Paudel S., Zacharioudakis IM., Zervou FN., Ziakas PD. and Mylonakis E. (2015)

ABSTRACT

Several factors including antibiotic use, immunosuppression and frequent hospitalizations make solid organ transplant (SOT) recipients vulnerable to Clostridium difficile infection (CDI). We conducted a meta-analysis of published studies from 1991-2014 to estimate the prevalence of CDI in this patient population. We searched PubMed, EMBASE and Google Scholar databases. Among the 75,940 retrieved citations, we found 30 studies coded from 35 articles that were relevant to our study. Based on these studies, we estimated the prevalence of CDI among 21,683 patients who underwent transplantation of kidney, liver, lungs, heart, pancreas, intestine or more than one organ and stratified each study based on the type of transplanted organ, place of the study conduction, and size of patient population. The overall estimated prevalence in SOT recipients was 7.4% [95%CI, (5.6-9.5%)] and it varied based on the type of organ transplant. The prevalence was 12.7%[95%CI, (6.4%- 20.9%)] among patients who underwent transplantation for more than one organ. The prevalence among other SOT recipients was: lung 10.8% [95% CI, (5.5%-17.7%)], liver 9.1 % [95%CI, (5.8%-13.2%)], intestine 8% [95% CI, (2.6%-15.9%)], heart 5.2% [95%CI, (1.8%-10.2%)], kidney 4.7% [95% CI, (2.6%-7.3%)], and pancreas 3.2% [95% CI, (0.5%-7.9%)]. Among the studies that reported relevant data, the estimated prevalence of severe CDI was 5.3% [95% CI (2.3%-9.3%)] and the overall recurrence rate was 19.7% [95% CI, (13.7%- 26.6%)]. In summary, CDI is a significant complication after SOT and preventive strategies are important in order to reduce the CDI related morbidity and mortality.

24. Fecal Microbiota Transplant for Treatment of Clostridium diffi cile Infection in Immunocompromised Patients

Am J Gastroenterol 2014; 109:1065–1071

Colleen R. Kelly et al

ABSTRACT

Objectives: Patients who are immunocompromised (IC) are at increased risk of *Clostridium diffi cile* infection (CDI), which has increased to epidemic proportions over the past decade. Fecal microbiota transplantation (FMT) appears effective for the treatment of CDI, although there is concern that IC patients may be at increased risk of having adverse events (AEs) related to FMT. This study describes the multicenter experience of FMT in IC patients.

Methods: A multicenter retrospective series was performed on the use of FMT in IC patients with CDI that was recurrent, refractory, or severe. We aimed to describe rates of CDI cure after FMT as well as AEs experienced by IC patients after FMT. A 32-item questionnaire soliciting demographic and pre- and post-FMT data was completed for 99 patients at 16 centers, of whom 80 were eligible for inclusion. Outcomes included (i) rates of CDI cure after FMT, (ii) serious adverse events (SAEs) such as death or hospitalization within 12 weeks of FMT, (iii) infection within 12 weeks of FMT, and (iv) AEs (related and unrelated) to FMT.

Results: Cases included adult (75) and pediatric (5) patients treated with FMT for recurrent (55 %), refractory (11 %), and severe and / or overlap of recurrent / refractory and severe CDI (34 %). In all, 79 % were outpatients at the time of FMT. The mean follow-up period between FMT and data collection was 11 months (range 3 – 46 months). Reasons for IC included: HIV / AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other medical conditions / medications (15). The CDI cure rate after a single FMT was 78 % , with 62 patients suffering no recurrence at least 12 weeks post FMT. Twelve patients underwent repeat FMT, of whom eight had no further CDI. Thus, the overall cure rate was 89 % . Twelve (15 %) had any SAE within 12 weeks post FMT, of which 10 were hospitalizations. Two deaths occurred within 12 weeks of FMT, one of which was the result of aspiration during sedation for FMT administered via colonoscopy; the other was unrelated to FMT. None suffered infections definitely related to FMT, but two patients developed unrelated infections and five had self-limited diarrheal illness in which no causal organism was identified. One patient had a superficial mucosal tear caused by the colonoscopy

25. Fecal Microbiota Transplantation for Refractory Clostridium difficile Colitis in Solid Organ Transplant Recipients

American Journal of Transplantation 2014; 14: 477–480

Friedman-Moraco R. J., Mehta A. K., Lyon G. M. and Kraft C. S.

ABSTRACT

Fecal microbiota transplantation (FMT) has been shown to be safe and efficacious in individuals with refractory *Clostridium difficile*. It has not been widely studied in individuals with immunosuppression due to concerns about infectious complications. We describe two solid organ transplant recipients, one lung and one renal, in this case report that both had resolution of their diarrhea caused by *C. difficile* after FMT. Both recipients required two FMTs to achieve resolution of their symptoms and neither had infectious complications. Immunosuppressed individuals are at high risk for acquisition of C. difficile and close monitoring for infectious complications after FMT is necessary, but should not preclude its use in patients with refractory disease due to *C. difficile*. Sequential FMT may be used to achieve cure in these patients with damaged microbiota from antibiotic use and immunosuppression.

26. Loss of Vancomycin-Resistant Enterococcus Fecal Dominance in an Organ Transplant Patient With Clostridium difficile Colitis After Fecal Microbiota Transplant

Open Forum Infectious Diseases 2015

Stripling J., Kumar R., Baddley J. W., Nellore A., Dixon P., Howard D., Ptacek T., Lefkowitz E. J., Tallaj J. A., Benjamin Jr W. H., Morrow C. D. and Martín Rodríguez J.

ABSTRACT

We report the use of fecal microbiota transplantation in a single heart-kidney transplant recipient with recurrent *Clostridium difficile*, vancomycin-resistant Enterococcus (VRE) fecal dominance, and recurrent VRE infections. Fecal microbiota transplantation resulted in the reconstruction of a diverse microbiota with (1) reduced relative abundance of *C difficile* and VRE and (2) positive clinical outcome.

27. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection A Randomized Trial

Ann Intern Med. 2016;165:609-616.

Kelly C. R. and Khoruts A.

ABSTRACT

Background: To date, evidence for the efficacy of fecal microbiota transplantation (FMT) in recurrent *Clostridium difficile* infection (CDI) has been limited to case series and open-label clinical trials.

Objective: To determine the efficacy and safety of FMT for treatment of recurrent CDI.

Design: Randomized, controlled, double-blind clinical trial. (ClinicalTrials.gov: NCT01703494)

Setting: Two academic medical centers.

Patients: 46 patients who had 3 or more recurrences of CDI and received a full course of vancomycin for their most recent acute episode.

Intervention: Fecal microbiota transplantation with donor stool (heterologous) or patient's own stool (autologous) administered by colonoscopy.

Measurements: The primary end point was resolution of diarrhea without the need for further anti-CDI therapy during the 8-week follow-up. Safety data were compared between treatment groups via review of adverse events (AEs), serious AEs (SAEs), and new medical conditions for 6 months after FMT. Fecal microbiota analyses were performed on patients' stool before and after FMT and also on donors' stool.

Results: In the intention-to-treat analysis, 20 of 22 patients (90.9%) in the donor FMT group achieved clinical cure compared with 15 of 24 (62.5%) in the autologous FMT group ($P = 0.042$). Resolution after autologous FMT differed by site (9 of 10 vs. 6 of 14 [$P = 0.033$]). All 9 patients who developed recurrent CDI after autologous FMT were free of further CDI after subsequent donor FMT. There were no SAEs related to FMT. Donor FMT restored gut bacterial community diversity and composition to resemble that of healthy donors.

Limitation: The study included only patients who had 3 or more recurrences and excluded those who were immunocompromised and aged 75 years or older.

Conclusion: Donor stool administered via colonoscopy seemed safe and was more efficacious than autologous FMT in preventing further CDI episodes.

28. Treatment of Recurrent and Severe Clostridium Difficile Infection

Annu. Rev. Med. 2015. 66:373–86

Keller J.J. and Kuijper E.J.

ABSTRACT

Clostridium difficile infection (CDI) is a serious complication of hospitalization and antibiotic use with a high mortality and very high costs. Despite appropriate treatment, a subset of patients develop chronic recurrent CDI. Some other patients develop severe and life-threatening colitis.The risk factors, pathogenesis, and treatment of recurrent CDI and severe CDI are discussed in this review. In particular, fecal microbiota transplantation (FMT) as a treatment strategy is outlined and a treatment algorithm incorporating FMT is described.

29. Clostridium difficile infection: a review of current and emerging therapies

Annals of Gastroenterology (2016) 29, 147-154

Ofosu A.

ABSTRACT

Clostridium difficile (*C. difficile*) infection (CDI) is the most common cause of healthcare-associated infections in US hospitals. The epidemic strain NAP1/BI/ribotype 027 accounts for outbreaks worldwide, with increasing mortality and severity. CDI is acquired from an endogenous source or from spores in the environment, most easily acquired during the hospital stay. The use of antimicrobials disrupts the intestinal microflora enabling *C. difficile* to proliferate in the colon and produce toxins. Clinical diagnosis in symptomatic patients requires toxin detection from stool specimens and rarely in combination with stool culture to increase sensitivity. However, stool culture is essential for epidemiological studies. Oral metronidazole is the recommended therapy for milder cases of CDI and oral vancomycin or fidaxomicin for more severe cases. Treatment of first recurrence involves the use of the same therapy used in the initial CDI. In the event of a second recurrence oral vancomycin often given in a tapered dose or intermittently, or fidaxomicin may be used. Fecal transplantation is playing an immense role in therapy of recurrent CDI with remarkable results. Fulminant colitis and toxic megacolon warrant surgical intervention. Novel approaches including new antibiotics and immunotherapy against CDI or its toxins appear to be of potential value.

30. An Update on Antimicrobial Resistance in Clostridium difficile: Resistance Mechanisms and Antimicrobial Susceptibility Testing

J. Clin. Microbiol 2017. doi:10.1128/JCM.02250-16

Peng Z., Jin D., Bum Kim H., Stratton C. W., Wu B., Tang Y. and Sun X.

ABSTRACT

Oral antibiotics such as metronidazole, vancomycin and fidaxomicin are therapies of choice for CDI. Several important mechanisms for *C. difficile* antibiotic resistance have been described; these include the acquisition of antibiotic resistance genes via transfer of mobile genetic elements, selective pressure *in vivo* resulting in gene mutations, altered expression of redox-active proteins, iron metabolism and DNA repair, as well as biofilm formation. This update summarizes new information published since 2010 on phenotypic and genotypic resistance mechanisms in *C. difficile* and addresses susceptibility test methods as well as other strategies to counter antibiotic resistance of *C. difficile*.

31. Drug-resistant cytomegalovirus in transplant recipients: a French cohort study

J Antimicrob Chemother 2010; 65: 2628–2640

Hantz S., Garnier-Geoffroy F. et al

ABSTRACT

Objectives: Cytomegalovirus (CMV) drug resistance is a therapeutic challenge in the transplant setting. No longitudinal cohort studies of CMV resistance in a real-life setting have been published in the valganciclovir era. We report findings for a French multicentre prospective cohort of 346 patients enrolled at initial diagnosis of CMV infection (clinical trial registered at clinicaltrials.gov: NCT01008540).

Patients and methods: Patients were monitored for detection of CMV infection for ≥2 years. Real-time detection of resistance by UL97 and UL54 gene sequencing and antiviral phenotyping was performed if viral replication persisted for .21 days of appropriate antiviral treatment. Plasma ganciclovir assays were performed when resistance was suspected.

Results: Resistance was suspected in 37 (10.7%) patients; 18/37 (5.2% of the cohort) had virological resistance, associated with poorer outcome. Most cases involved single UL97 mutations, but four cases of multidrug resistance were due to UL54 mutations. In solid organ transplant recipients, resistance occurred mainly during primary CMV infection (odds ratio 8.78), but also in two CMV-seropositive kidney recipients. Neither CMV prophylaxis nor antilymphocyte antibody administration was associated with virological resistance.

Conclusions: These data show the feasibility of surveying resistance. Virological resistance was frequent in patients failing antiviral therapy. More than 1/5 resistant isolates harboured UL54 mutations alone or combined with UL97 mutations, which conferred a high level of resistance and sometimes were responsible for crossresistance, leading to therapeutic failure.

32. Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection

Transplantation 2016;100: e74–e80

Avery R. K. and Arav-Boger R.

ABSTRACT

Background. Antiviral-resistant or refractory cytomegalovirus (CMV) infection is challenging, and salvage therapies, foscarnet, and cidofovir, have significant toxicities. Several investigational anti-CMV agents are under development, but more information is needed on outcomes of current treatments to facilitate clinical trial design for new drugs.

Methods. Records of solid organ transplant (SOT) and hematopoietic cell transplant (HCT) recipients at a single center over a 10-year period were reviewed retrospectively to characterize those who had received foscarnet treatment for ganciclovir-resistant or refractory CMV infection. Data were collected on virologic responses, mortality, and nephrotoxicity.

Results. Of 39 patients (22 SOT, 17 HCT), 15 had documented ganciclovir resistance mutations and 11 (28%) of 39 had tissue-invasive CMV. Median duration of foscarnet was 32 days. Virologic failure occurred in 13 (33%) of 39 and relapses of viremia occurred in 31%. Mortality was 12 (31%) of 39 and was higher in HCT than SOT (P = 0.001), although ganciclovir resistance was more common in SOT (P = 0.003). Doses of ganciclovir or valganciclovir were low in 10 (26%) of 39 at some time before switching to foscarnet. Renal dysfunction occurred in 20 (51%) of 39 by end of treatment and in 7 (28%) of 25 after 6 months.

Conclusions. Outcomes of existing treatment for ganciclovir-resistant or refractory CMV are suboptimal, in terms of virologic clearance, renal dysfunction, and mortality. These data should provide background information for future clinical trials of newer antiviral agents.

33. Successful outcome of ganciclovir-resistant cytomegalovirus infection in organ transplant recipients after conversion to mTOR inhibitors

Transplant International ª 2012 European Society for Organ Transplantation 25 (2012) e78–e82

Sabé N., González-Costello J., Rama I., Niubó J., Bodro M., Roca J., Cruzado J M., Manito N. and Carratala J.

Summary

Ganciclovir-resistant (GanR) cytomegalovirus (CMV) infection after organ transplantation is emerging as a significant therapeutic challenge. We report two cases of GanR CMV infection successfully managed by switching immunosuppression from calcineurin inhibitors to an mTOR inhibitor-based regimen. This salvage therapy should be considered when other options are not available.

34. Detection of cytomegalovirus drug resistance mutations in solid organtransplant recipients with suspected resistance

Journal of Clinical Virology 90 (2017) 57–63

López-Aladida R., Guiua A., Sanclemente G. et al

ABSTRACT

Background: Current guidelines recommend that treatment of resistant cytomegalovirus (CMV) in solid organ transplant (SOT) recipients must be based on genotypic analysis. However, this recommendation is not systematically followed.

Objectives: To assess the presence of mutations associated with CMV resistance in SOT recipients with suspected resistance, their associated risk factors and the clinical impact of resistance.

Study design: Using Sanger sequencing we prospectively assessed the presence of resistance mutations in a nation-wide prospective study between September 2013-August 2015.Results: Of 39 patients studied, 9 (23%) showed resistance mutations. All had one mutation in the UL97 gene and two also had one mutation in the UL54 gene. Resistance mutations were more frequent in lung transplant recipients (44% p = 0.0068) and in patients receiving prophylaxis ≥6 months (57%vs. 17%, p = 0.0180). The mean time between transplantation and suspicion of resistance was longer inpatients with mutations (239 vs. 100 days, respectively, p = 0.0046) as was the median treatment duration before suspicion (45 vs. 16 days, p = 0.0081). There were no significant differences according to the treatment strategies or the mean CMV load at the time of suspicion. Of note, resistance-associated mutations appeared in one patient during CMV prophylaxis and also in a seropositive organ recipient. Incomplete suppression of CMV was more frequent in patients with confirmed resistance.

35. Incidence and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infections in 1244 Kidney Transplant Recipients

Transplantation 2011;92: 217–223

Myhre H., Dorenberg D. H., Kristiansen K. I., Torbjorn Leivestad H. R., Åsberg A. and Hartmann A.

ABSTRACT

Background. Cytomegalovirus (CMV) infections in kidney transplant recipients are in most cases successfully treated with oral valganciclovir (VGCV). However, in a few percent of patients, mutations in the *UL 97* or *UL 54* gene lead to drug resistance.

Methods. We investigated the incidence and outcomes of ganciclovir-resistant CMV viremia in all 1244 kidney recipients transplanted at our center from 2004 through 2008. CMV DNAemia was monitored in all patients at least weekly, and patients who were positive were treated preemptively with VGCV (900 mg once daily).

Results. Ganciclovir-resistant mutations were detected in 27 patients (2.2%), of which 26 occurred in the 209 CMV IgG-negative recipients receiving a CMV-positive kidney (12.5%). All had *UL97* gene mutations, and none had *UL54* gene mutations. Mean DNAemia half-life for the first (nonresistance) episode ofCMV viremia was 3.8±1.2 days. After established resistance, 25 of 27 patients had their mycophenolate mofetil dose reduced by approximately 50%, and 10 of these were also treated with intravenous foscarnet. The DNAemia half-life was 3.7_1.4 days in the foscarnet-treated patients, significantly shorter than in the other 17 patients, 10.8±6.7 days (*P*_0.001). Time to DNAemia eradication was 30±16 and 81±51 days in the two groups, respectively (*P*_0.001).

Conclusion. Use of 900 mg VGCV once daily for preemptive CMV treatment is associated with a high incidence of CMV *UL97*-resistance gene mutations in D_/R_ patients. Foscarnet treatment rapidly and safely eradicated CMV DNAemia, and also patients who only reduced the immunosuppression and continued on VGCV treatment eventually cleared the virus.

36. Adoptive T Cell Immunotherapy for Treatment of Ganciclovir-Resistant Cytomegalovirus Disease in a Renal Transplant Recipient

American Journal of Transplantation 2015; 15: 827–832

Macesic N., Langsford D., Nicholls K. et al

ABSTRACT

Cytomegalovirus (CMV) is a significant cause of morbidity, mortality and graft loss in solid organ transplantation (SOT). Treatment options for ganciclovir-resistant CMV are limited. We describe a case of ganciclovir-resistant CMV disease in a renal transplant recipient manifested by thrombotic microangiopathyassociated glomerulopathy. Adoptive T cell immunotherapy using CMV-specific T cells from a donor bank was used as salvage therapy. This report is a proof-of-concept of the clinical and logistical feasibility of this therapy in SOT recipients.

37. Leflunomide: a treatment option for ganciclovir-resistant cytomegalovirus infection after renal transplantation

NDT Plus (2009) 2: 149–151

Andrassy J., Illner W. D., Rentsch M., Jaeger G., Jauch K. W. and Fischereder M.

ABSTRACT

Cytomegalovirus (CMV) infection after renal transplantation is a problem of increasing concern resulting in significant morbidity and mortality. Wide spread use of ganciclovir (GCV) and valganciclovir (VGCV) may cause an increase of CMV resistance to these first line drugs. Other treatment options are sparse and often complicated by adverse events, namely nephrotoxicity associated with foscarnet and cidofovir. Leflunomide may be another treatment option for CMV infections. So far it is not clear if leflunomide can also be used in the case of GCV-resistant CMV infections. Here we describe the use of leflunomide in two patients after renal transplantation with GCV-resistant CMV infections.

38. The use of sirolimus in ganciclovir-resistant cytomegalovirus infections in renal transplant recipients.

Clin Transplant 2007; 21: 675–680

Ozaki KS., Camara NO., Nogueira E. et al.

ABSTRACT

Background: The widespread use of prophylactic ganciclovir and anti-lymphocyte/thymocyte therapies are associated with increased induction of ganciclovir-resistant cytomegalovirus (CMV) strains. The use of sirolimus has been associated with a lower incidence of CMV infection in transplant recipients. We questioned whether it could also be effective as a therapeutic treatment of resistant CMV infection.

Methods: Patients with ganciclovir-resistant CMV infections determined clinically and by DNA sequencing analysis were enrolled. Antigenaemia and DNA sequencing were used to diagnosis and follow the mutations.

Results: Nine transplant patients were given sirolimus plus mycophenolate mofetil (n = 4) or a calcineurin inhibitor (n = 5). Seven out of nine recipients were CMV IgG negative before transplantation. We observed a rapid decrease in antigenaemia levels, reaching zero in eight out of nine (88.9%) patients within a median of 20.3 ± 10.1 d. Graft function remained stable and no patient presented acute rejection or recurrence of the CMV infection.

Conclusions: This suggests that the use of sirolimus plus ganciclovir therapy could be useful in ganciclovir-resistant CMV infections.

39. Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet.

J Clin Virol 2006; 37: 124–127

Drew WL., Miner RC., Marousek GI. et al.

ABSTRACT

Background: The cytomegalovirus (CMV) UL97 inhibitor drug maribavir (MBV) is undergoing clinical antiviral trials.

Objectives*:* To assess the MBV sensitivity of CMV strains and isolates containing mutations that confer resistance to current antiviral drugs ganciclovir, cidofovir or foscarnet.

Study design: Resistant clinical isolates and laboratory strains containing UL97 and or UL54 DNA polymerase mutations were tested for sensitivity to all four drugs by standard plaque reduction assay and a reporter-based yield reduction assay. Sensitive control strains were also tested.

Results: Eleven CMV strains or isolates resistant to GCV, four resistant to FOS and two resistant to CDV, were all sensitive to MBV. These viruses represent four UL97 mutations and three UL54 DNA polymerase mutations. The laboratory derived UL97 L397R mutant was highly MBV-resistant but remained sensitive to the other three drugs.

Conclusions: No cross-resistance has been detected between viruses resistant to MBV and those resistant to one or more of the current CMV antiviral drugs, consistent with differences in their mechanisms of action.

40. Antibiotic-resistant priority pathogens list

Virtual press conference, 27 February 2017 (complet script)

41. Infection in Organ Transplantation

American Journal of Transplantation 2017; 17: 856–879

Fishman J. A.

ABSTRACT

The prevention, diagnosis, and management of infectious disease in transplantation are major contributors to improved outcomes in organ transplantation. The risk of serious infections in organ recipients is determined by interactions between the patient's epidemiological exposures and net state of immune suppression. In organ recipients, there is a significant incidence of drug toxicity and a propensity for drug interactions with immunosuppressive agents used to maintain graft function. Thus, every effort must be made to establish specific microbiologic diagnoses to optimize therapy. A timeline can be created to develop a differential diagnosis of infection in transplantation based on common patterns of infectious exposures, immunosuppressive management, and antimicrobial prophylaxis. Application of quantitative molecular microbial assays and advanced antimicrobial therapies have advanced care. Pathogen-specific immunity, genetic polymorphisms in immune responses, and dynamic interactions between the microbiome and the risk of infection are beginning to be explored. The role of infection in the stimulation of alloimmune responses awaits further definition. Major hurdles include the shifting worldwide epidemiology of infections, increasing antimicrobial resistance, suboptimal assays for the microbiologic screening of organ donors, and virus-associated malignancies. Transplant infectious disease remains a key to the clinical and scientific investigation of organ transplantation.

42. Progressive increase of resistance in Enterobacteriaceae urinary isolates from kidney transplant recipients over the past decade: narrowing of the therapeutic options

Transpl Infect Dis 2016: 18: 575–584

Origüen J., Fernández-Ruiz M., López-Medrano F., et al.

ABSTRACT

Background: Antibiotic resistance is an emerging phenomenon in kidney transplantation (KT).

Methods: We compared species distribution and antimicrobial susceptibility patterns in 1052 isolates from urine cultures obtained in 2 different cohorts of kidney transplant recipients in a single center (Cohort A: 189 patients undergoing KT between January 2002 and December 2004 [336 isolates]; Cohort B: 115 patients undergoing KT between January 2011 and December 2013 [716 isolates]).

Results: Asymptomatic bacteriuria accounted for most of the isolates (86.9% in Cohort A and 92.3% in Cohort B). *Klebsiella pneumoniae* (9.5% vs. 15.6%), *Pseudomonas aeruginosa* (1.8% vs. 7.9%), and *Enterobacter cloacae* (0.6% vs. 3.1%) were significantly more common in Cohort B. The isolation of K. *pneumoniae* in Cohort B was associated with the occurrence of acute pyelonephritis (9.8% of all *K. pneumoniae* isolates vs. 2.8% of the remaining uropathogens; P = 0.001). Non-susceptibility rates among Enterobacteriaceae in Cohort B were higher for every class of antibiotics (P ≤ 0.003) with the exception of fosfomycin. Compared to Cohort A, significant increases were seen in isolates from Cohort B for multidrugresistant (MDR) (43.9% vs. 67.8%, respectively; P = 0.001), extendedspectrum beta-lactamase (ESBL)-producing (6.6% vs. 26.1%; P = 0.001), and carbapenemase-producing Enterobacteriaceae strains (0.0% vs. 5.0%; P = 0.001). Such differences were mostly attributable to *K. pneumoniae* (as 54.5% and 13.4% of isolates in Cohort B were ESBL-producing and carbapenemase-producing, respectively). MDR isolates were responsible for 69.1% of episodes of symptomatic urinary tract infection in Cohort B.

Conclusion: The increase in resistance rates among Enterobacteriaceae uropathogens is significant and may have an effect on KT programs.

43. Multidrug-resistant bacterial infection in solid organ transplant recipients

Enferm Infecc Microbiol Clin. 2012;30(Supl 2):40-48

Cervera C., Linares L., Bou G. and Moreno A.

ABSTRACT

The most frequent complication from infection after solid organ transplantation is bacterial infection. This complication is more frequent in organ transplantation involving the abdominal cavity, such as liver or pancreas transplantation, and less frequent in heart transplant recipients. The sources, clinical characteristics, antibiotic resistance and clinical outcomes vary according to the time of onset after transplantation. Most bacterial infections during the first month post-transplantation are hospital acquired, and there is usually a high incidence of multidrug-resistant bacterial infections. The higher incidence of complications from bacterial infection in the first month post-transplantation may be associated with high morbidity. Of special interest due to their frequency are infections by *S. aureus*, enterococci, Gram-negative enteric and non-fermentative bacilli. Opportunistic bacterial infections may occur at any time on the posttransplant timeline, but are more frequent between months two and six, the period in which immunosuppression is higher. The most frequent bacterial species causing opportunistic infections in organ transplant recipients are *Listeria monocytogenes* and *Nocardia* spp. After month six, posttransplantation solid organ transplant patients usually develop conventional community-acquired bacterial infections, especially urinary tract infections by *E. coli* and *S. pneumoniae* pneumonia. In this article we review the clinical characteristics, epidemiology, diagnosis and prognosis of bacterial infections in solid organ transplant patients.

44. Preemptive Versus Sequential Prophylactic-Preemptive Treatment Regimens for Cytomegalovirus in Renal Transplantation: Comparison of Treatment Failure and Antiviral Resistance

Transplantation 2010;89: 320–326

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ABSTRACT

Background: Cytomegalovirus (CMV) infections after transplantation are commonly treated using a prophylactic or preemptive regimen with (val)ganciclovir. It remains unclear, which approach is most effective in preventing CMV disease in D+R- patients. The aim of this retrospective study was to compare the treatment response and antiviral resistance in CMV infections between two treatment regimens in D+R- renal transplant recipients.

Methods: Before 2006, a preemptive treatment regimen with valganciclovir was applied (42 patients). From 2006 onwards, patients first received prophylaxis with valganciclovir for 90 days, followed by a preemptive regimen (29 patients). CMV infections were monitored by regular determination of the CMV DNA load in plasma. Patient charts were reviewed for antiviral treatment data, and resistance was analyzed by nucleotide sequence analysis of the *UL97* and *UL54* genes in CMV DNA-positive samples.

Results: Treatment failure, defined as a CMV DNA load more than or equal to 1000 copies/mL after at least 2 weeks of treatment, occurred less frequently in the prophylaxis cohort than in the preemptive cohort (14% vs. 71%, *P*_0.001). No CMV end-organ disease occurred in either cohort. Resistant viral isolates were found during treatment in one patient in the prophylaxis cohort versus in three patients in the preemptive group. All CMV infections with resistant virus were cleared without switch of (val)ganciclovir treatment.

Conclusions: Treatment failure of CMV infections occurred less frequently in D+R- renal transplant patients on a sequential prophylaxis-preemptive regimen than in patients on a purely preemptive regimen. Antiviral resistance was observed infrequently and apparently played a minor role in treatment failure.

45. Contribution of next generation sequencing to early detection ofcytomegalovirus UL97 emerging mutants and viral subpopulationsanalysis in kidney transplant recipients

Journal of Clinical Virology 80 (2016) 74–81

Garrigue I., Moulinas R., Recordon-Pinson P. et al.

ABSTRACT

Background: Cytomegalovirus (CMV) is the major opportunistic virus encountered after transplantation, and resistant variants challenge antiviral treatment. We studied the emergence and evolution of the canonical UL97 L595S mutation in four kidney recipients by comparing Sanger sequencing with a specific next-generation sequencing (NGS) assay, and assessed the global evolution of *UL97* gene variability.

Study design: Plasmids harbouring wild-type and/or L595S mutated *UL97* genes were used to assess the analytical performances of NGS assay. *UL97* gene was retrospectively analysed in patients' samples drawn during CMV infection follow-up, Shannon entropy (Sn) was calculated and phylogenetic analyses were performed.

Results: Wild-type and L595S plasmids PCR products were mixed to obtain L595S concentrations of0, 1, 2, 5, 10, 20 and 100%. Mean triplicate NGS results were 0, 0.71, 1.79, 5.30, 13.17, 17 and 100%,respectively, while Sanger sequencing only detected L595S when above 20%. The NGS mean error rate was 0.196 ± 0.07%. In the four patients, emergence of L595S mutation under ganciclovir treatment was followed-up. After foscarnet rescue therapy, leading to undetectable CMV viral load, in two patients,L595S mutant re-emerged, but was only detected by NGS technology (14% and 9.6%). Using NGS data, phylogenetic trees and Sn showed a complex evolution of concomitant viral subpopulations.

Conclusions: NGS technology allowed a deeper discrimination of the emergence and persistence of a drug resistance mutation, which could be pertinent to investigate when routine Sanger sequencing detects only wild-type strains. Moreover, NGS improved sensitivity helps in studying viral abundance, dynamics and diversity, less approachable with Sanger sequencing.

46. Global Action Plan on Antimicrobial Resistance

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