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ORIGINAL ARTICLE

Group milleri streptococci: significant pathogens in solid organ recipients

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Summary

Group milleri streptococci (GMS) comprise a heterogeneous group of streptococci including the species *intermedius*, *constellatus* and *anginosus*. They may cause chronic intra-abdominal and intrathoracic abscesses, which are difficult to treat. This is a retrospective analysis including 45 transplant recipients in whom GMS were isolated. The epidemiology, clinical significance and the impact on the outcome in all transplant patients with infections caused by GMS during a 4-year period (2001–2004) was evaluated. The 45 solid organ recipients (88 isolates) included 34 liver-, four kidney/pancreas-, one kidney-, two small bowel-, three combined liver/kidney- and one combined kidney/small bowel transplant recipient. In 42 cases GMS caused intra-abdominal infection, in two cases pleural empyema and in one case soft tissue infection. Only a single isolate of GMS was cultured from blood. In 54 of the 88 specimens (61%), which grew GMS, other pathogens were also isolated. GMS frequently caused recurrent cholangitis ($n = 17$) associated with anastomotic and nonanastomotic biliary strictures. These cases were managed by repeated stenting or surgical intervention and prolonged antibiotic therapy. No patient died directly related to GMS infection and all except one case responded to combined surgical/antibiotic treatment. One pancreas graft was lost because of erosion haemorrhage associated with an abscess. GMS were susceptible to penicillin G, carbapenems and clindamycin, whereas cephalosporins and quinolones showed intermediate activity or resistance in some cases, and GMS in general were found resistant to aminoglycosides. GMS may cause serious infections in transplant recipients which are difficult to treat. Their prevalence in transplant surgical site infections thus far may have been underestimated.

Introduction

Long-term results after solid organ transplantation (SOT) have constantly improved by advances in surgical techniques, immunosuppressive therapy, antirejection treatment and better prophylaxis and treatment of infectious complications. Infections remain common causes of post-transplant morbidity and mortality [1,2]. The spectrum of bacterial pathogens in transplant surgery largely depends on the source of the infection and is more diverse than in the normal host, including not only common germs such as staphylococci and enterococci, enterobactericcae and nonfermentative bacilli, but also rare pathogens such as *Nocardia* spp., *Legionella* spp. and *Listeria monocytogenes* amongst others [1–4]. Streptococci seem to be uncommon causing agents. One relevant subgroup of streptococci is a member of the group milleri streptococci (GMS), which are characterized by a high potential to

cause purulent infection and abscess formation. GMS comprise a subset of streptococci such as the species *Streptococcus intermedius*, *Streptococcus constellatus*, *Streptococcus anginosus* together with rare β-haemolytic streptococci of Lancefield groups G and F. GMS are commensals of the respiratory, intestinal and urogenital tract [5–7]. Following translocation into otherwise sterile sites, they may cause purulent infections. The clinical relevance of GMS is based on the propensity for deep abscess formation, requiring surgical intervention and drainage. Penetration of many antibiotics, which are *in vitro* active against GMS, into these abscesses is poor. This makes therapy even more difficult [5–9]. Little is known about the significance of GMS in transplant recipients.

This article describes our experience with all infections caused by GMS in transplant recipients ($n = 45$), which were identified during a 4-year period.

Patients and methods

Patients

Between 2001 and 2004, a total of 1029 solid organ transplants were performed at the Innsbruck Medical University Hospital. This included 502 renal, 231 liver, 127 pancreas, 80 cardiac, 57 lung, 11 intestinal, 19 islet and two hand transplants. In this series, 45 patients were identified with GMS infection.

Immunosuppression

Immunosuppression consisted of a calcineurin inhibitor (CNI)-based triple drug therapy, consisting of either cyclosporin A (CsA) or tacrolimus (TAC) in combination with azathioprine (AZA) or mycophenolate mofetil (MMF) and rapidly tapered steroids. ATG or IL-2-receptor antibody basiliximab induction was administered in all cardiac, lung and intestinal recipients. In renal and liver recipients induction was used according to the individual immunological risk and as part of a renal-sparing protocol.

Antimicrobial prophylaxis

Antibacterial prophylaxis consisted of penicillin G in combination with flucloxacillin or of ceftriaxon for kidney recipients. Piperacillin/tazobactam was used in heart, liver, pancreas and small bowel recipients, and cefepime in lung recipients. Antifungal prophylaxis consisted of fluconazole for pancreas recipients and of liposomal amphotericin B for patients at risk for filamentous fungal infection. Anti-CMV prophylaxis using (val)ganciclovir was given in the case of CMV mismatch transplantation and in the case of intensified immunosuppression. *Pneumocystis jiroveci* pneumonia prophylaxis consisted of trimethoprim/sulfamethoxazol for heart and lung recipients and a subset of recipients of other organs if they were included in multicentre trials.

Microbiological analysis

Isolation and identification of GMS at our microbiological laboratory followed the guidelines of the Clinical and Laboratory Standards Institute (CLSI). All specimens were cultured aerobically and anaerobically. Specimens were incubated on Columbia agar containing 5% sheep red blood cells and incubated in a CO_2-enriched atmosphere for 48 h. Isolated streptococci were identified by morphology, colony size and haemolysis pattern. Identification of GMS was made with API 20 Strep Bio Merieux® (Marcy-lÈtoile, France) which includes *S. anginosus*, *S. constellatus*, *S. intermedius* and certain β-haemolytic streptococci from Lancefield groups C, F and G. Subtyping was not performed. Antimicrobial susceptibility testing was performed using the disc diffusion assay according to CLSI guidelines (CLSI 2004 Performance Standards for Antimicrobial Susceptibility Testing; Fourteenth Informational Supplement CLSI, Wayne, PA, USA).

Identification of patients, data collection and statistical analysis

All results of microbiological specimen testing at our hospital are archived in a computerized database. This database was searched for all isolates of GMS identified between January 2001 and December 2004. A total of 436 000 samples were processed at our microbiological facility during the study period and 637 GMS-positive isolates in 452 patients were identified. The computerized database of the transplant surgical department was matched with the identified patients from the microbiology database and a total of 45 solid organ recipients with GMS infections were identified, which represents 10% of all patients with GMS infection. Clinical data of these patients were retrieved from the existing transplant database, electronic records and hospital paper charts. Data are reported as a total number and percentage or mean ± standard deviation (SD).

Results

Microbiological specimen analysis

Of the 451 GMS-positive patients, 246 (54.4%) were treated on surgical wards including 5.7% from transplant surgery. Nonsurgical patients accounted for 45.6% of GMS infections. Within this group, 19% of patients were treated on Internal Medicine with the vast majority of patients being treated on the Department of Gastroenterology and Hepatology. A total

of 88 isolates of GMS were isolated in the 45 solid organ recipients. Table 1a and b displays the spectrum of specimens from which GMS were isolated together with the type of organ the patients were transplanted.

Clinical data

The 45 study patients were 20 female (36.4%) and 25 male (63.6%) patients with a median age of 53.6 years (range 1.1–69.9). There were 34 liver-, three liver/kidney, two small bowel, one small bowel/kidney, four pancreas/kidney and one kidney recipient. Sites of infection were pleural cavity in two cases, soft tissue infection in one case and intra-abdominal infection in 42 cases. Of all intra-abdominal infection, 79.2% was cholangitis, the remaining were intra-abdominal abscesses (9.3%), spontaneous peritonitis (2.3%) and peritonitis secondary to perforation (9.2%). Only a single isolate of GMS was cultured from blood. In 54 of the 88 specimens (61%), which grew GMS, other pathogens were also isolated. There were 38 isolates of Gram-negative rods, three isolates of nonfermentative bacilli, 24 isolates of Gram-positive cocci, two isolates of Gram-positive rods, nine isolates of anaerobic bacteria and two isolates of yeast. The spectrum of pathogens isolated together with GMS is shown in detail in Table 2.

Therapy of GMS infection

Surgery and endoscopic interventions

In 17 patients, GMS caused recurrent cholangitis associated with anastomotic and nonanastomotic biliary strictures. In one case, this led to sepsis and this was the only case in which GMS were isolated from blood cultures. Cholangitis associated with cholangiopathy was managed by repeated stenting ($n = 15$) and prolonged antibiotic therapy. In most cases the infection was polymicrobial. In one case surgical revision of the biliary anastomosis was performed, in one case the necrotic liver segment III was resected and the biliary anastomosis revised, and in one case cholangitis led to graft failure and this patient deceased during the retransplant caused by septic shock and primary nonfunction of a split graft, which was accepted from another institution.

Surgical interventions were performed in 20 patients (44%), including laparotomy in nine patients. Percutaneous drainage of intra-abdominal abscesses was performed in two patients. The two patients with GMS pleural empyema were treated with pleural drainage. The procedures are displayed in detail in Table 3.

Antimicrobial therapy

Most commonly used antimicrobial agents were penicillins such as amoxicillin/clavulanic acid or piperacillin/tazobactam, carbapenems, cephalosporins, clindamycin and ciprofloxacin (Fig. 1). Ciprofloxacin was the preferred

Table 1. (a) Group milleri streptococci (GMS) infections according to the transplanted organ. (b) Spectrum of GMS infections in solid organ recipients.

(a)	
Liver TX	34
Liver/kidney TX	3
Pancreas/kidney TX	4
Small bowel TX	2
Kidney TX	1
Small bowel/kidney TX	1
(b)	
Thoracic infection	2
Pleural empyema	4.4%
Intra-abdominal infection	43
Hepato-biliary tract	79.2%
Upper GI tract	4.6%
Lower GI tract	4.6%
Intra-abdominal abscesses	9.3%
Ascites	2.3%

Table 2. Spectrum of pathogens isolated together with group milleri streptococci.

Gram-negative rods	38
Escherichia coli	11
Proteus mirabilis	1
Morganella morgagnii	2
Klebsiella spp.	11
Enterobacter spp.	11
Citrobacter freundii	1
Serratia spp.	1
Nonfermentative bacilli	3
Pseudomonas spp.	3
Gram-positive rods	24
Coagulase-negative staphylococci	6
Staphylococcus aureus	1
Enterococcus fecalis	15
Enterococcus faecium	2
Anaerobes/others	11
Bacteroides spp.	9
Lactobacillus spp.	2
Fungi	2
Candida spp.	2

Table 3. Surgical interventions caused by group milleri streptococci infection.

Hartman's procedure	1
Laparotomy, drainage, lavage	7
Closure of perforated duodenal ulcer	1
Revision of biliary anastomosis	2
Liver re-transplantation	1
Percutaneous abscess drainage	6
Pleural drainage	2

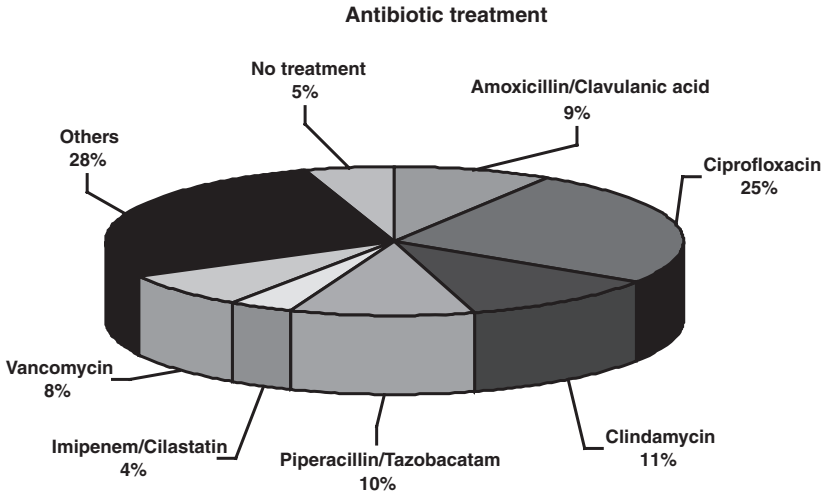

Figure 1 Spectrum of applied antibiotics for treatment of group milleri streptococci in SOT.

antimicrobial agent that was applied by the gastroenterologists in the case of cholangitis. Median time of antibiotic therapy was 12 days (range 1–32).

Patient outcome

No patient died directly related to GMS infection and all except one case responded to combined surgical/antibiotic treatment. Two pancreatic grafts were lost because of erosion haemorrhage of the arterial anastomosis associated with an abscess. One patient died during liver re-transplantation and during follow-up another four patients died, including three intestinal recipients and one liver recipient. All other patients recovered; however, 22 patients (49%) developed recurrent infections.

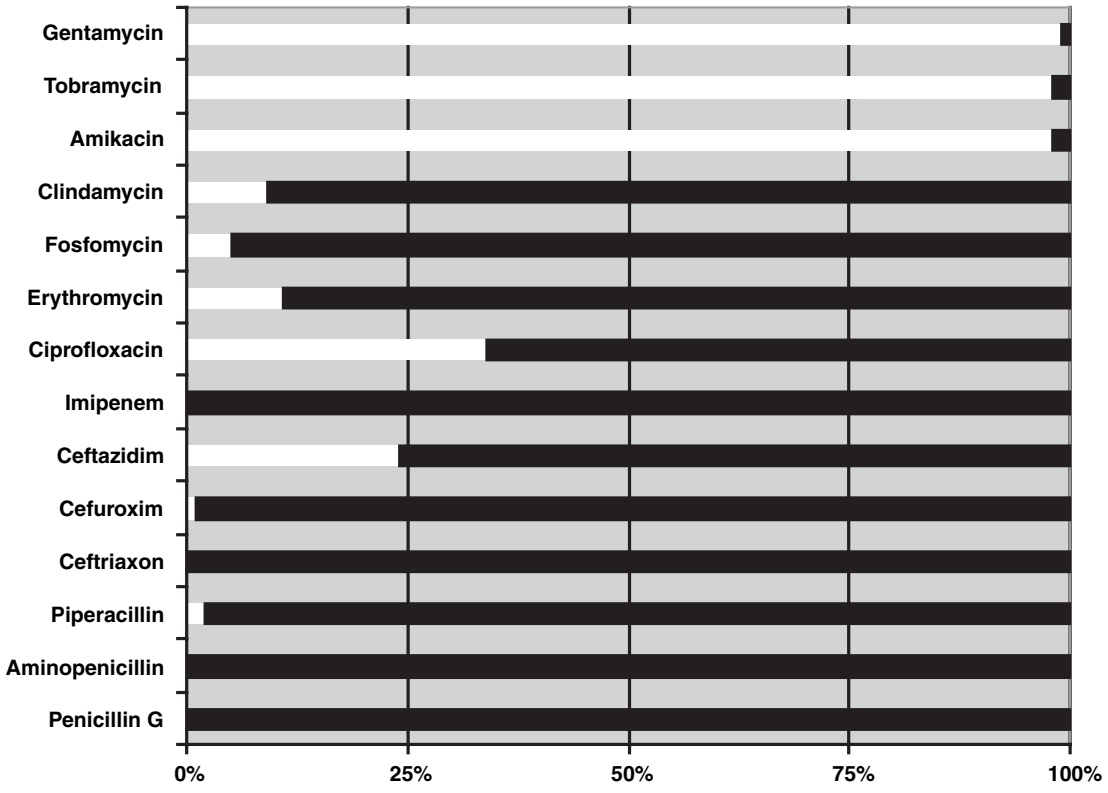

Figure 2 Results from sensitivity testing from the 88 group milleri streptococci isolates.

Results of antibiotic susceptibility testing

Group milleri streptococci isolates were susceptible to penicillin, imipenem/cilastatin and cephalosporins in 75–100%. Clindamycin was active in 91%, fosfomycin in 94% and ciprofloxacin in 69%. All strains were resistant to aminoglycosides (Fig. 2).

Discussion

This case series gives evidence that GMS may play a more important role in transplant infectious diseases than thus far estimated. The pathogen is mainly found in intra-abdominal infections and in particular, cholangitis in the setting of cholangiopathy post-liver transplantation, this pathogen may be of importance. As ciprofloxacin traditionally has been advocated by gastroenterologists when performing interventions of the biliary tract and this agent is not particularly active – at least *in vivo* – against GMS, a change in the antibiotic prophylaxis/therapy in this case to a penicillin or clindamycin may be indicated. Intestinal recipients also may be a risk group for these infections.

Group milleri streptococci are commensals of the respiratory, intestinal and urogenital tract [6,7,10,11]. Following translocation into otherwise sterile sites, they may cause purulent infections [8]. Very little information is available concerning GMS infections in transplant recipients, and in most cases GMS infections were reported within the series of other infections.

The clinical relevance of GMS in transplant surgery is based on the propensity for deep abscess formation, requiring surgical intervention and drainage. An important aspect is the immunosuppressive therapy which may facilitate progression of the infection even if only a low inoculum of pathogens is present such as spilled contaminated bile or small bowel contents in the case of biliary anastomosis, or small bowel reconstruction [12,13].

Group milleri streptococci infections mandate high-dose antibiotic treatment and pharmacokinetic issues have to be considered as penetration of antibiotics into abscesses may be poor. Our preferred antibiotic for GMS soft tissue infections and intra-abdominal infections (IAI) is clindamycin and in most cases, combination with a betalactam antibiotic or quinolone is used [6,14–16]. Clindamycin may have some advantages in terms of pharmacokinetics as the agent accumulates intracellularly within white blood cells and it can be delivered to the site of infection even in the case of abscess membranes which is commonly found in GMS infections [15,17,18].

For biliary infections, traditionally quinolones have been suggested by gastroenterologists, in particular during endoscopic interventions. However, GMS are in general not very sensitive to quinolones and there may be discrepancies between *in vitro* and *in vivo* activity [15,17].

In addition to antibiotic therapy, evacuation of infected collections must be performed. This may include drainage of pleural empyema, intra-abdominal abscesses or even abscesses within the liver. In the case of mechanical cholestasis the bile must be drained either by endoscopic retrograde cholangiopancreatography (ERCP), PTC or surgical intervention. Notably, drainage of abscesses also allows for accurate diagnosis and enables optimal antibiotic therapy [12–14].

Group milleri streptococci are pathogens that are mainly found in surgical infections. The clinical presentation in many cases is severe and recurrence of the infection is common. It must be considered that GMS require more intense and longer therapy than many other pathogens. Moreover, mixed infection must be expected and local hydrolysis of betalactam antibiotics by betalactamases produced by other pathogens may occur [5,6,11,15]. Therefore, combination antibiotic therapy is our policy in these infections.

In conclusion, we found that GMS infection may be more common in transplant recipients than thus far considered. Of all our diagnosed cases of GMS within the entire hospital, 10% was in transplant recipients. The highest prevalence was found in liver recipients with cholangitis and in intestinal recipients with intra-abdominal infections.

References

1. Cuellar-Rodriguez J, Sierra-Madero JG. Infections in solid organ transplant recipients. *Rev Invest Clin* 2005; **57**: 368.
2. Bassetti M, Righi E, Bassetti D. Antimicrobial prophylaxis in solid-organ transplantation. *Expert Rev Anti Infect Ther* 2004; **2**: 761.
3. Wiesmayr S, Stelzmueller I, Tabarelli W, *et al*. Nocardiosis following solid organ transplantation: a single-centre experience. *Transpl Int* 2005; **18**: 1048.
4. Wiesmayr S, Tabarelli W, Stelzmueller I, *et al*. Listeria meningitis in transplant recipients. *Wien Klin Wochenschr* 2005; **117**: 229.
5. Piscitelli SC, Shwed J, Schreckenberger P, Danziger LH. Streptococcus miller group: renewed interest in an elusive pathogen. *Eur J Clin Microbiol Infect Dis* 1992; **11**: 491.
6. Clarridge JE, Attorri S, Musher DM, *et al*. *Streptococcus intermedius*, *Streptococcus constellatus* and *Streptococcus anginosus* (''*Streptococcus milleri* group'') are of different clinical importance and are not equally associated with abscess. *J Clin Infect Dis* 2001; **32**: 1511.
7. Belko J, Goldmann DA, Macone A, Zaidi AK. Clinically significant infections with organisms of the *Streptococcus milleri* group. *Pediatr Infect Dis J* 2002; **21**: 715.

8. Tachopoulou OA, Vogt DP, Henderson JM, Baker M, Keys TF. Hepatic abscess after liver transplantation: 1990–2000. *Transplantation* 2003; **75**: 79.
9. Stelzmueller I, Hoeller E, Wiesmayr S, *et al*. Severe intra-abdominal infection due to *Streptococcus milleri* following adjustable gastric banding. *Obes Surg* 2005; **15**: 576.
10. Sugihara E, Kido Y, Okamoto M, *et al*. Clinical features of acute respiratory infections associated with the *Streptococcus milleri* group in the elderly. *Kurume Med J* 2004; **51**: 53.
11. Whiley RA, Beighton D, Winstanley TG, Fraser HY, Hardie JM. *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* (the *Streptococcus milleri* group): association with different body sites and clinical infections. *J Clin Microbiol* 1992; **30**: 243.
12. Zoepf T, Maldonado-Lopez EJ, Hilgard P, *et al*. Balloon dilatation vs. balloon dilatation plus bile duct endoprostheses for treatment of anastomotic biliary strictures after liver transplantation. *Liver Transpl* 2006; **12**: 88.
13. Zoepf T, Maldonado-Lopez EJ, Hilgard P, *et al*. Endoscopic therapy of posttransplant biliary stenoses after right-sided adult living donor liver transplantation. *Clin Gastroenterol Hepatol* 2005; **3**: 1144.
14. Porta G, Rodriguez-Carbellaira M, Gomez L, *et al*. Thoracic infection caused by *Streptococcus milleri*. *Eur Respir J* 1998; **12**: 357.
15. Yamamoto N, Kubota T, Tohyama M, *et al*. Trends in antimicrobial susceptibility of the *Streptococcus milleri* group. *J Infect Chemother* 2002; **8**: 134.
16. Salavert M, Gomez L, Rodriguez-Carballeira M, Xercavins M, Freixas N, Garau J. Seven-year review of bacteremia caused by *Streptococcus milleri* and other viridans streptococci. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 365.
17. Tracy M, Wanahita A, Shuhatovich Y, Goldsmith EA, Clarridge JE 3rd, Musher DM. Antibiotic susceptibilities of genetically characterized *Streptococcus milleri* group strains. *Antimicrob Agents Chemother* 2001; **45**: 1511.
18. Piscitelli SC, Shwed J, Schreckenberger P, Danziger LH. *Streptococcus milleri* group: renewed interest in an elusive pathogen. *Eur J Clin Microbiol Infect Dis* 1992; **11**: 491.

