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Infections post transplant

Changing pattern of bacterial susceptibility to antibiotics in hematopoietic stem cell transplant recipients

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Summary:

Adequate infection prophylaxis and empirical antibiotic therapy are of critical importance after hematopoietic stem cell transplantation (HSCT). We examined the evolution of bacterial susceptibility to antibiotics in 492 patients (198 allografts and 294 autografts) transplanted between 1982 and 1999 and evaluated whether ciprofloxacin prophylaxis and an empirical antibiotic regimen (glycopeptide + third-generation cephalosporin) were still valid. We collected all susceptibility tests performed during the initial hospitalization on blood cultures as well as routine surveillance cultures and analyzed susceptibility to ciprofloxacin and to major antibiotics used in our unit. Gram-positive cocci rapidly became resistant to ciprofloxacin (susceptibility around 70% in 1990 to less than 20% in 1998) but sensitivity to glycopeptides remained unaltered. There was a rapid decline in the number of patients colonized with Gram-negative bacilli in the early years of ciprofloxacin prophylaxis. However, susceptibility to ciprofloxacin fell sharply from around 90% in 1990 to around 30% in 1999. In parallel, susceptibility to ceftazidime also decreased to less than 80% in recent years. Piperacillin (± tazobactam) did not show any variation over time and its efficacy remained too low (about 60%). Imipenem as well as recently introduced cefepim and meropenem showed stable and excellent profiles (>90% susceptibility). In conclusion: (1) quinolone prophylaxis has now lost most of its value; (2) the choice of a third-generation cephalosporin for empirical antibiotic therapy may no longer be the best because of the emergence of Gram-negative strains resistant to β-lactamases, such as Enterobacter sp. More appropriate regimens of empirical antibiotic therapy in HSCT recipients may be based on the use of a carbapenem or fourth-generation cephalosporin.

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Infections are still one of the major sources of complications after hematopoietic stem cell transplantation (HSCT). About 50 to 60% of febrile episodes are thought to be related to an infectious process and one-third of these are caused by bacterial infection.[1,2] Major sites of infection include the gastrointestinal tract, respiratory tract and skin.[2]

To lower this risk of infection, a number of measures are taken, including the use of antibiotics such as quinolones. However, the value of quinolone prophylaxis has been questioned in recent years.[2–6] In addition, it has become standard practice to use empiric antibiotic therapy whenever a bacterial infection is suspected. However, there has always been a lot of controversy about the most appropriate antibiotic regimen to use in this setting.[2,7–11] On the basis that on the one hand the most frequent bacterial infectious episodes are due to Gram-positive bacteria, but that on the other hand the most severe ones are caused by Gram-negative organisms, since 1991 we elected to use a combination of a glycopeptide (vancomycin) and a third-generation cephalosporin (ceftazidime).

In 2000, we conducted an evaluation of our policy of prophylactic and empiric antibiotic therapy. For this purpose, we collected all susceptibility tests performed on all surveillance and diagnostic bacterial cultures in 492 consecutive recipients of an HSC transplant between 1982 and 1999. We classified the most frequent bacteria encountered into five categories and examined the evolution over time of their sensitivity to the quinolone (ciprofloxacin) used as prophylaxis and to the i.v. antibiotics most frequently used in our department. This analysis resulted in major changes in our policy, including abandoning quinolone prophylaxis and changing our choice of empiric antibiotic therapy.

Patients and methods

We collected data from 492 consecutive recipients of an HSC transplant performed between 1982 and 1999 in our department. The 17 years of follow-up were divided into eight consecutive periods, each including about 60 patients: period 1 (1982 to September 1987: old hospital), period 2 (October 1987 (new hospital) to 1990), period 3 (1991 to 1992), period 4 (1993 to 1994), period 5 (1995 to 1996), period 6 (1997), period 7 (1998) and period 8 (1999). Ciprofloxacin prophylaxis (500 mg twice daily orally) was introduced in period 3. The empiric antibiotherapy regi-

mens used were amikacin + piperacillin (1982–1990) and ceftazidime + vancomycin (1991–1999). Imipenem has been used as the second-line empiric regimen. Median age at time of transplant was 37 years, ranging from 10 months to 66 years. There were 198 allografts (40% of cases) and 294 autografts (60% of cases). There were 235 females (48%) and 257 males (52%). For allotransplants, the source of stem cells was bone marrow ($n = 154$), peripheral blood ($n = 40$) or cord blood ($n = 4$). Autotransplants were done with PBSC ($n = 217$), bone marrow ($n = 45$) or both ($n = 32$). The population described consisted of patients suffering from non-neoplastic disorders ($n = 17$), AML ($n = 107$), NHL ($n = 75$), multiple myeloma ($n = 63$), ALL ($n = 56$), CML ($n = 47$), myelodysplastic syndromes ($n = 17$), Hodgkin's disease ($n = 16$), breast cancer ($n = 66$) or other solid tumours ($n = 28$). Eighty-seven patients (18%) died during their initial hospitalization. Overall, 54% of patients are alive and 46% died. Over 50% of them died of their original disease and 11% of infection.

We collected all susceptibility tests performed on all surveillance and diagnostic bacterial cultures performed during the whole initial hospitalization. Routine surveillance cultures were carried out twice a week on a set of samples obtained from various body sites (nose, throat, tongue, sputum, skin, penis, vagina, stools, anus and urine). In some cases, it is possible that bacteria present at different sites or at different time points actually represented the same strain. In cases of simultaneous occurrence at various sites, the laboratory generally provided only one susceptibility test, but it is possible that the same strain was occasionally counted twice when detected at two different time points after transplantation. Finally, to better separate colonizing from invasive microorganisms, we carried out a separate analysis of susceptibility to all bacteremias.

Bacteria were classified into four categories, taking into account both their relative frequency and their biological characteristics. These four categories were Coagulase-negative Staphylococci, Enterococci, Streptococci and Gram-negative bacilli. We could not consider *Staphylococcus aureus* because only 14 isolates were found throughout the study period. For Enterococci and Streptococci, data were collected on six antibiotics: ampicillin, vancomycin, teicoplanin, imipenem, amikacin and ciprofloxacin. For coagulase-negative Staphylococci, the same antibiotics were evaluated, except that ampicillin was replaced by oxacillin. For Gram-negative bacilli, we compared piperacillin (alone or in association with Tazobactam), ceftazidime, cefepim, imipenem, meropenem, aztreonam, amikacin and ciprofloxacin. The antibiotics analyzed were the ones most frequently used in our department for empiric or specific therapy, plus ciprofloxacin which was used prophylactically. Identification and antimicrobial susceptibility testing were performed according to the manufacturer's recommendations by using the SCEPTOR system (BD, Brussels, Belgium) in 1982–1992 or the automated VITEK system since 1993 (BioMerieux, St Louis, MO, USA). MICs were determined and interpretation category results (susceptible, intermediate and resistant) were also routinely provided. Interpretation criteria were based on updated NCCLS (National Committee for Clinical Laboratory Standards) breakpoints. Classification into sensitive and resistant strains was done on the basis of MIC.

Results

Enterococci (Table 1)

Table 1 describes the evolution of the sensitivity of enterococci to the six selected antibiotics. Vancomycin and teicoplanin retain a nearly 100% efficacy throughout the periods (only one strain resistant to vancomycin in period 3). Sensitivity to ampicillin is a little lower ($P < 0.0001$) but remains stable at over 90%. The number of strains tested for imipenem or amikacin in the latest periods is too small to draw any firm conclusion. Sensitivity to ciprofloxacin is lower ($P < 0.0001$) and has substantially declined ($P = 0.0091$) from periods 2–3 (57%) to periods 4–5 (39%) to periods 6–7 (20%), although it is more favourable in the last period.

There were only seven Enterococci bacteremias. Susceptibility to vancomycin, teicoplanin and ampicillin was 100% while that to ciprofloxacin (33%) and amikacin (20%) were lower.

Streptococci (Table 2)

The small number of strains tested does not allow adequate data interpretation. The available evidence indicates no particular trend over time, with an excellent sensitivity to vancomycin and ampicillin but significantly lower sensitivity to amikacin ($P < 0.0001$) or ciprofloxacin ($P < 0.0001$).

There were 22 bacteremias due to Streptococci. Sensi-

Table 1 Enterococci

	All		*Period 1*		*Period 2*		*Period 3*		*Period 4*		*Period 5*		*Period 6*		*Period 7*		*Period 8*	
	n tested	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*
Ampicillin	340	92	77	94	16	94	61	97	102	86	20	90	9	100	35	100	20	90
Vancomycin	333	99.6	72	100	22	100	59	98	95	100	23	100	8	100	35	100	19	100
Teicoplanin	96	100	0		0		20	100	10	100	8	100	3	100	35	100	20	100
Imipenem	15	100	14	100	0		0		1	100	0		0		0		0	
Amikacin	143	47	71	49	15	27	26	46	6	100	2	100	4	50	16	25	3	67
Ciprofloxacin	185	46	0		6	67	59	56	56	38	13	46	5	20	36	19	20	65

Table 2 Streptococci

	All		Period 1		Period 2		Period 3		Period 4		Period 5		Period 6		Period 7		Period 8	
	n tested	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*
Ampicillin	58	95	7	100	16	88	10	90	6	100	5	100	4	100	5	80	5	100
Vancomycin	70	96	13	77	18	100	13	100	6	100	6	100	4	100	5	100	5	100
Teicoplanin	0		0		0		0		0		0		0		0		0	
Imipenem	3	100	2	100	1	100	0		0		0		0		0		0	
Amikacin	53	58	12	83	17	47	7	29	3	100	2	50	3	67	5	60	4	50
Ciprofloxacin	37	51	0		7	57	10	50	5	60	4	75	3	0	4	50	4	50

Table 3 Coagulase-negative Staphylococci

	All		Period 1		Period 2		Period 3		Period 4		Period 5		Period 6		Period 7		Period 8	
	n tested	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*
Oxacillin	1273	26	394	34	226	27	218	8	251	15	56	5	51	10	54	24	23	13
Vancomycin	1243	99.5	358	99.7	236	100	220	99.5	241	100	61	97	50	100	54	100	23	100
Teicoplanin	185	99	0		1	100	56	100	23	91	21	100	12	100	49	100	23	100
Imipenem	103	80	76	82	25	72	0		0		1	100	0		1	100	0	
Amikacin	659	63	418	69 0	160	60	0		0		5	100	0		53	36	23	30
Ciprofloxacin	762	20	0		110	52	229	14	243	13	62	8	51	8	54	31	23	17

tivity to vancomycin (100%) and ampicillin (89%, NS) were excellent, but this was low to amikacin (40%, $P < 0.0001$) and ciprofloxacin (28%, $P < 0.0001$). There was no change over time.

Coagulase-negative Staphylococci (Tables 3 and 4)

Vancomycin and teicoplanin always maintained excellent results and, as for Enterococci, resistance to glycopeptides remained extremely rare (Table 3). Soon after its introduction, there was a very rapid and major loss of sensitivity to ciprofloxacin in periods 3–6 (14% compared to 52% in period 2, $P < 0.0001$), although some recovery was observed in periods 7–8 (27%, $P = 0.0005$ compared to periods 3–6). Oxacillin is now ineffective in over 80% of cases ($P < 0.0001$) and sensitivity to amikacin has also declined seriously from periods 1–2 to periods 7–8 ($P < 0.0001$).

There were 116 bacteremias caused by coagulase-negative staphylococci (Table 4). Susceptibility results parallel those observed with all strains (Table 3) for vancomycin (NS), teicoplanin (NS) and amikacin (NS), but sensitivities to ciprofloxacin ($P < 0.0001$) and oxacillin ($P = 0.0015$) are a little superior for bacteria isolated from blood cultures.

Gram-negative bacilli (Tables 5 and 6)

After a sustained decrease in the incidence of Gram-negative bacteria through period 5, the number of strains has increased again in recent years (Table 5). In particular, Pseudomonas strains have become very rare. The results of period 1 should be interpreted with caution because at that time cefotaxime was sometimes tested instead of ceftazidime. Susceptibility to ciprofloxacin has fallen from 93% when it was introduced, to 32% in 1999 ($P < 0.0001$). Ceftazidime has also lost some of its efficacy, decreasing from

Table 4 Bacteremias with coagulase-negative Staphylococci

	All		Period 1		Period 2		Period 3		Period 4		Period 5		Period 6		Period 7		Period 8	
	n tested	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*	*n tested*	% *sensitive*
Oxacillin	116	40	14	57	16	62	23	43	11	36	23	26	9	33	15	33	5	0
Vancomycin	115	100	13	100	16	100	23	100	11	100	23	100	9	100	15	100	5	100
Teicoplanin	24	100	0		0		2	100	2	100	1	100	1	100	13	100	5	100
Imipenem	11	100	0		9	100	0		0		0		0		2	100	0	
Amikacin	38	58	14	64	14	86	0		0		0		0		6	50	4	0
Ciprofloxacin	97	47	0		11	100	23	43	11	36	23	48	9	11	15	60	5	0

Table 5 Gram-negative bacilli

	All		*Period 1*		*Period 2*		*Period 3*		*Period 4*		*Period 5*		*Period 6*		*Period 7*		*Period 8*	
	n tested	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*
Piperacillin	781	60	303	50[a]	189	79	53	70	121	55	26	65	45	60	14	71	30	37
Tazobactam	153	75	0		0		0		0		0		12	100	73	73	68	74
Ceftazidime	823	84	245	76[a]	169	97	52	89	99	90	21	100	69	78	95	79	73	71
Imipenem	508	94	106	94	77	94	6	100	82	89	20	90	58	95	89	100	70	91
Aztreonam	463	81	1	100	76	88	44	84	116	85	21	86	48	69	86	78	71	79
Amikacin	920	93	307	91	171	95	53	98	128	95	22	100	71	89	94	97	74	84
Ciprofloxacin	533	58	0		95	93	51	65	127	47	27	59	69	61	89	48	71	32
Cefepim	148	94	0		0		0		0		0		13	100	70	99	65	88
Meropenem	129	95	0		0		0		0		0		3	100	66	100	60	90

[a]Testing was often done for cefotaxime instead of ceftazidime and ticarcillin instead of piperacillin.

94% in periods 2–5 to 76% thereafter ($P < 0.0001$). Further comparison of periods 2–5 *vs* periods 6–8 demonstrates moderate but significant reductions in the sensitivity of Gram-negative bacilli to piperacillin (69% *vs* 54%, $P = 0.0053$), aztreonam (86% *vs* 76%, $P = 0.0064$) and amikacin (96% *vs* 90%, $P = 0.0064$), but stable values for imipenem (91% *vs* 96%, NS). This emergence of resistant strains is partly related to Enterobacter species but also to a few Pseudomonas strains in the last period. Finally, cefepim and meropenem maintain their efficacy to >90% since their introduction. We also examined the susceptibility to a combination of ceftazidime + amikacin. Among 316 doubly tested strains, 96% were sensitive to either antibiotic, but this has tended to decrease in recent years (99% for periods 2–5 versus 90% for periods 6–8 (80% in period 8), $P = 0.0002$). For the combination of amikacin + cefepim, the figure for periods 6–8 was 96% (NS). The susceptibility of Gram-negative bacilli now remains excellent for imipenem, meropenem or cefepim, while ceftazidime, aztreonam and piperacillin with or without tazobactam are entirely insufficient.

There were 52 bacteremic episodes with Gram-negative bacilli (Table 6). These isolates tended to be less susceptible to ceftazidime (61% *vs* 84%, $P < 0.0001$), aztreonam (61% *vs* 81%, $P = 0.0094$) and imipenem (83% *vs* 94%, $P = 0.0202$), but more sensitive to ciprofloxacin (85% *vs* 58%, $P = 0.0023$) than those found in surveillance cultures. Figures were comparable for piperacillin and amikacin, but the numbers were too low to allow interpreting meropenem, cefepim and tazobactam sensitivities.

Discussion

We conducted a retrospective survey on the evolution of bacteria sensitivity to major antibiotics used as prophylaxis or empiric therapy in recipients of a hematopoietic stem cell transplant in our transplantation unit between 1982 and 1999. Several interesting results emerged. Since the introduction of quinolone prophylaxis, there has been a rapid emergence of resistant strains of Gram-positive as well as Gram-negative bacteria. On the other hand, whereas we did not encounter Gram-positive bacteria that were resistant to glycopeptides, a significant proportion of Gram-negative bacteria became resistant to the third-generation cephalosporin used in our empirical antibiotic schedule, although some of these resistant strains would be sensitive to the addition of amikacin. These results were rather similar among strains isolated from surveillance cultures or from blood cultures obtained during bacteremias. These observations should bring about major changes in our prophylactic and therapeutic policy.

Table 6 Bacteremias with Gram-negative Bacilli

	All		*Period 1*		*Period 2*		*Period 3*		*Period 4*		*Period 5*		*Period 6*		*Period 7*		*Period 8*	
	n tested	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*	*n tested*	*% sensitive*
Piperacillin	46	63	12	8[a]	5	80	4	100	3	100	9	78	9	89	0		4	50
Tazobactam	7	71	0		0		0		0		0		0		3	100	4	50
Ceftazidime	52	61	12	8[a]	6	66	4	100	5	100	9	67	9	100	3	100	4	25
Imipenem	30	83	4	75	1	100	3	67	1	100	5	80	9	100	3	100	4	75
Aztreonam	28	61	0		3	66	2	100	4	25	5	80	7	86	3	33	4	25
Amikacin	50	86	12	83	5	100	4	75	5	80	8	88	9	100	3	100	4	50
Ciprofloxacin	33	85	0		0		4	100	5	100	8	75	9	100	3	100	4	25
Cefepim	5	80	0		0		0		0		0		0		3	100	2	50
Meropenem	6	83	0		0		0		0		0		0		3	100	3	67

[a]Testing was often done for cefotaxime instead of ceftazidime and ticarcillin instead of piperacillin.

Sensitivity of Gram-positive bacteria to ciprofloxacin has fallen dramatically in the years following its systematic use as prophylaxis in our unit. This is in keeping with the findings of previous studies.[3–6] Likewise, Gram-negative bacteria, including Pseudomonas as well as Enterobacteriacae, have also developed a high degree of resistance to quinolones. These observations should make us abandon the use of quinolone prophylaxis. Indeed, although quinolone prophylaxis has been shown in the past to efficiently reduce the incidence of Gram-negative bacteremia, it has allowed the development of resistance and has never been associated with a reduction in infection-related mortality.[2–6] However, the problem of resistance not only stems from quinolone use in transplant patients but from their more widespread use in these patients during induction or salvage chemotherapy before stem cell transplantation. Therefore, it cannot be excluded that a more targeted use of quinolone prophylaxis in transplant recipients only could regain some interest in the future.

The frequency and severity of infections is inversely related to neutrophil counts and duration of aplasia. Furthermore, bacteriological identification tests are not fast, sensitive and/or specific enough, although molecular biology techniques may improve this situation in the future.[2] Many infections cannot be documented sufficiently early or even at all, and therefore early use of empirical antibiotic therapy is necessary in severely neutropenic patients. An empirical schedule should be chosen on the basis of cost, potential side-effects, development of resistance and pattern of infections in a particular type of patient.[1] In 1997, the Infectious Diseases Society of America established international guidelines for first-line antibiotic therapy in neutropenic patients with fever of undetermined origin.[2] There were three possible schedules: (1) ceftazidime + vancomycin (if a glycopeptide is necessary); (2) monotherapy with ceftazidime or imipenem (or with cefepim or meropenem); (3) anti-Pseudomonas β-lactam + aminoglycoside. The value of the third schedule is debatable. First, while one of its advantages was supposed to be its faster bactericidal action, monotherapy with a carbapenem resulted in responses that occurred with the same delay.[7] Second, although the association of a β-lactam and an aminoglycoside was thought to be synergistic, response rates of this classical schedule or a monotherapy were shown to be identical.[7] Finally, whereas a previous study indicated that this association could lower the risk of resistance,[8] another report showed that the addition of an aminoglycoside to imipenem did not prevent the emergence of imipenem-resistant Pseudomonas.[12]

The emergence of multiresistant Gram-negative bacteria in our patient population is in part related to the occurrence of Enterobacter sp. in recent years. Infection by a multiresistant Enterobacter is correlated in 69% of cases with previous administration of a β-lactam and above all a third-generation cephalosporin.[13–18] Therefore, based on our epidemiology and on literature data showing that monotherapies seem to be as efficient and well tolerated as classical associations,[7] it is clear that we have to change our empirical antibiotic therapy regimen and replace ceftazidime with either a fourth-generation cephalosporin or a carbapenem. On the other hand, our *in vitro* data for Gram-negative bacilli would suggest that the addition of amikacin to ceftazidime would enhance the efficacy of this empiric regimen. However, as susceptibility to this association has decreased in recent years, the combination of cefepim and amikacin would appear to be preferable in our patient population.

In addition, the use of a glycopeptide in a first-line empirical regimen should be abandoned. The current literature is unanimous on that point.[13,19–23] Although the number of Gram-positive bacteremias has increased in neutropenic patients, vancomycin has never been shown to reduce the mortality rate when it is used empirically. Even if it is not (yet) the case in our unit, the emergence of resistant Gram-positive enterococci in the US[7–9] should incite us to limit the use of vancomycin to cases where bacteriological documentation or a clinical argument (catheter infection, known colonization, mucositis) exist. Both vancomycin and teicoplanin remain perfect choices for the treatment of infections with coagulase-negative staphylococci, enterococci and streptococci in our unit.

From the results of our retrospective survey, major changes should be implemented in our unit, including abandoning quinolone prophylaxis and modifying our standard regimen of empiric antibiotic therapy. These changes may not be adequate for other hospitals because they need to be based on the local epidemiology. However, it is obvious that a thoughtful policy of antibiotic therapy should be in place in every transplant unit because a time relationship between antibiotic use and resistance has been well established and it is in departments which use antibiotics the most that the prevalence of resistant bacteria is the highest.[5,7,12–14,16,17,19,24] There is no unique solution for the control of resistant strains but some steps can be considered[12,13,20,25,26] including constitution of an information and surveillance team, careful monitoring of the use of key antibiotics, staff education, and periodic rotation among systemic antibiotics with different modes of action.

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