Multidrug-resistant *Pseudomonas aeruginosa* out break in the Haematological Unit of a 79-year old Cancer Institute

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Background

Pseudomonas aeruginosa remains a major pathogen among febrile neutropenic patients; empirical antibiotic treatment for febrile neutropenia covers since many decades *Pseudomonas aeruginosa*, since the mortality due to infections occurring in this setting is high(1,2). In the era of antibacterial resistance, the latest data from ECDC (European Centre for Disease Prevention and Control) suggest that *Pseudomonas aeruginosa* acquires resistance to almost all traditional anti-pseudomonas drugs: aminoglycosides, ceftazidime, fluoroquinolones, piperacillin/tazobactam and carbapenems, especially in Southern and Eastern Europe(3). CDC (Centers for Disease Control and Prevention) estimated in 2013, that 51.000 healthcare-associated *Pseudomonas aeruginosa* infections occurred in USA hospitals; more than 6.000(13%) of those are multidrug-resistant, with roughly 400 deaths per year attributed to these infections (4). Identifying and treating correctly patients with multidrug-resistant *Pseudomonas aeruginosa* is a major concern for clinicians, microbiologists and infection control teams; patients with severe defects of immunity, such as the cancer/haematological patients represent a particular subgroup, since the initiation of the correct antimicrobial treatment is crucial to their survival. On the other hand, detecting the source of multidrug-resistant *Pseudomonas aeruginosa* and enhancing antimicrobial stewardship becomes urgent in the absence of new antibacterial agents in the pharma pipeline (5,6). In September 2013, the Infectious Diseases Team and the Infection Control Team of our institution were notified of one case of invasive multidrug-resistant *Pseudomonas* infection in an allo-PBSC recipient during medullary aplasia following the engraftment (after conditioning chemotherapy).

Methods(i)

1. Setting: The Haematology Unit of the Jules Bordet Institute(B3) as constructed in 1988.

6 rooms with anteroom and laminar flow-5 rooms with anteroom.1 room without anteroom. The water sources in the patient's rooms /anterooms were equipped with « total germ filters » (tabs: AQ31F1R; shower bulbs:AQF4) provided by PALL Corporation. The water sources outside these locations were not protected

2. Index case: Invasive multidrug-resistant *Pseudomonas aeruginosa* infection associated with sepsis was diagnosed in 2013 in an allo-PBSC(peripheral blood stem cells) patient during medullary aplasia. The patient developed ARDS(acute respiratory distress syndrome) requiring his transfer to a specialized center for ECMO(Extracorporeal membrane oxygenation); tailored antimicrobial treatment, optimal supportive treatment and bone marrow recuperation were mandatory in the successful management of a severely immunocompromised patient. In the weeks following this case, 3 more haematological patients from the same unit were detected with the same multidrug-resistant *Pseudomonas aeruginosa* in clinical samples. These cases triggered a thorough investigation in order to detect the source of multi-drug resistant *Pseudomonas aeruginosa*, to establish an adequate therapeutic regimen and implement preventive measures.

3. Observations: The observations were conducted in the Haematology Unit: the patients, the medical staff, nurses, paramedical personnel and cleaning team as well the water environment of the Unit were carefully evaluated in order to define the potential source of *Pseudomonas* contamination.

4. Microbiology: Bacteriological samples from the sanitary devices, water samples, samples from mouthwash solutions and parenteral nutrition were performed in the whole haematological unit, while active microbiological surveillance among patients was reinforced. The clinical samples of multidrug-resistant *Pseudomonas aeruginosa* were tested in the Belgian National Reference Center (NRC) for Antibiotic-resistant Gram-negative Bacilli (CHU Dinant-Godinne UCL Namur (Y. Glupczynski, T.D. Huang) and Hpital Erasme ULB Brussels (O. Denis)).

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Results(the patients)

Sex-Age	Diagnosis	Admitted for...	Time to become positive (days)	Neutropenia (>7d)/FN	Positive biological sample	Sepsis	Previous admissions in HU (<1month)	Quinolone prophylaxis	AB	Outcome
M-23	MA	alloPBSC	14	Y/Y	SC+blood	Y	Y	Y	Y	S
M-35	ALL	chemo�	5	N/N	Urine	N	Y	N	Y	S
F-38	AML	alloPBSC	17	Y/Y	SC+urine	N	Y	N	Y	S
F-69	AML	chemo�	56	Y/Y	Urine	N	N	Y	Y	S
M-30	AML	alloPBSC	13	Y/Y	SC	Y	N	Y	Y	S
F-49	MDS	alloPBSC	25	Y/Y	SC	N	Y	N	Y	S
M-65	AML	chemo�	0	Y/Y	SC	N	Y	N	Y	D
M-62	NHL	Renal failure	0	N/N	Urine	N	N	N	N	S
M-65	MDS	alloPBSC	17	Y/N	SC+blood	N	N	Y	Y	S
F-57	MF	alloPBSC	21	Y/Y	SC	Y	N	Y	Y	D
F-43	AML	alloPBSC	10	Y/Y	SC+blood	N	N	Y	Y	S
M-59	AML	chemo�	17	Y/Y	SC	Y	N	N	Y	D
M-53	AML	chemo�	17	Y/Y	SC	Y	N	N	Y	D
F-42	HL	GVHD	99	N/N	SC	N	N	N	Y	S
M-47	AML	alloPBSC	12	Y/Y	blood	Y	N	Y	Y	D

MA=medullary aplasia, ALL=acute lymphoblastic leukaemia, AML=acute myeloid leukaemia, MDS=myelodysplastic syndrome, NHL=non-Hodgkin lymphoma, HL=Hodgkin Lymphoma, alloPBSC=allogeneic peripheral blood stem cells graft, GVHD=graft-versus-host disease, SC=surveillance cultures (nose, throat, mouth, axilla, inguinal trough, anal, vaginal), Y=yes, N=no, S=survived, D=deceased

Fifteen patients were identified with multidrug-resistant *Pseudomonas aeruginosa* during a 2-year period. The majority of them were colonized, while 4 of them developed intractable sepsis during neutropenia followed by death. Molecular testing confirmed their genetic similarity: they all belonged to the same strain(AF1-2).

Results (the environment)

Pseudomonas aeruginosa, *Pseudomonas putida*, *Pseudomonas* spp and multidrug-resistant *Pseudomonas aeruginosa*-multi(R) were found in the doctor's office, in the nurse's office and in the 12 rooms of the Haematology Unit. The local strain was found in the restrooms of rooms 3,4 and in the sink (used by the patients in room). The water samples were positive for *Pseudomonas* spp. In the flush toilets of rooms 7,8,12, public toilets and the water tap at the entrance of the Haematology Unit.

Belgian National Reference Center (NRC) for Antibiotic-resistant Gram-negative bacilli (CHU Dinant-Godinne UCL Namur (Y. Glupczynski, T.D. Huang) and Hpital Erasme ULB Brussels (O. Denis)).→*Pseudomonas aeruginosa* (genomic macrorestriction (speI) PFGE typing):Type AF2, AF2 - P.MLSTpyo⇒horizontal transmission

Implementation of a Care Bundle

The douchettes used for cleaning the bedpans/urinals were eliminated(Fig.1). The flush toilets were gradually replaced and the recipients were disinfected once a week with Incidin active. The toilet brushes were replaced at every new patient. The toilet lids were replaced where needed. An automatic bedpan washer(ARCANIA AO600) was installed in the Haematological Unit and the management of excreta (faeces and urine) was thoroughly reviewed; a specific procedure was created and bedpans/urinals were specifically attributed to each patient during his stay. The strainers and the siphons of the sinks located in the patients' rooms, the anterooms/airlock lobbies and in the public areas (doctor's and nurse's office, public toilets) were replaced(Fig.2,3). A new anti-reflux insert by Aqua free was introduced, replaced once a month (or every new patient admitted) and disinfected, initially once a week, later once a day with Umonium 0.5%→ Incidin active (Fig.4). The "vidoir" was re-organized in order to accommodate the bedpan washer and to define the circulation of "dirty"- "clean" material (Fig. 5,6). The rooms were disinfected with the "Coccinelle H2O2" before a new patient entered the room. The showers were banned. The evacuation columns were preventively cleaned, in order to avoid the accidental toilet blocking and inundation with sewage water. The replacement of the sanitations and the realization of heavy plumber work were not feasible due to the enormous cost and the concomitant construction of the New Jules Bordet Institute. The patients were educated in toileting without a shower by using a basin; they were also reminded that sinks are designed for washing hands and other usages were discouraged. They were instructed as to how to collect faeces for analysis and to close the lid before flushing the toilet. The personnel of the Haematological Unit, including the cleaning personnel were highly solicited for learning and applying the new procedures, while refreshment of existing procedures was organized with the local "Rfrant d'hygine" in collaboration with the nurses of the Infection Control Team. Internal audits were realized in order to verify the adherence of the personnel in the new procedures. Close collaboration with the local microbiology laboratory and BRULABO was maintained and environmental/water samples were realized regularly (according to the availability of these partners).

Discussion(i)

This outbreak of multidrug-resistant *Pseudomonas aeruginosa* linked to water/health care facilities is just one more contribution in an already rich literature dedicated to *Pseudomonas aeruginosa* and frail patients: neonates, ICU and burns patients. The interaction between water, hospital waste systems, health-care professionals, hospital environment and patients is well-known and described. The *Pseudomonas aeruginosa* (multidrug-resistant or not) is implicated in numerous outbreaks attributed to tap water (7), health workers' hands (8), contaminated incubators, respiratory therapy equipment (9), feeding bottles (10), hand soap lotions (11), sanitary installations/plumbing (12,13). Defining the specific paths of contamination may be extremely difficult: in wards like neonate ICU, adult ICU, Burns Unit and Haematology the selection imposed by using broad spectrum antibiotics is high and the emergence of multidrug-resistant bacteria is vertiginous (with *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacteriaceae* being the leading causes) (4). Thus the question of who is contaminating who is crucial: are the patients that contaminate their environment via their excreta or is the environment that contaminates the patients via the water and the installations related to water? The modern molecular tools, such as PFGE (pulsed field gel electrophoresis), MLST (multilocus sequence typing), and WGS (Whole genome sequencing) are in favour of a dissemination from the environment to the patients via the water (14,13,15,16). The water facilities remain a major concern inside and outside the hospital: whirlpools, hot tubs, swimming pools and water slides (17) are involved in *Pseudomonas aeruginosa* outbreaks as well as old and new hospitals (12,13).

In our hospital, we tried to formulate the following question: is the water-related environment in the Haematological Unit responsible for this multidrug-resistant *Pseudomonas aeruginosa* outbreak? The water systems were old enough to be suspected and there is a rich literature supporting our hypothesis. It is obvious that in our setting the investigations had to be extremely broad and everything related to water had to be verified. The presence of *Pseudomonas aeruginosa* (as well as *Pseudomonas putida* and other *Pseudomonas* spp.) in taps, toilets and flush toilets, siphons, sinks and inserts was definitively demonstrated and confirmed the penchant of *Pseudomonas aeruginosa* for moist environment, water, limestone deposits and waste outlets. The clinical consequences of these findings were not negligible since four patients died with intractable sepsis and three of them had septicmia with the same strain of multidrug-resistant *Pseudomonas aeruginosa* in different time points.

On the other hand, solutions broadly used in the Haematology Unit, such as mouthwashes, total parenteral intravenous preparations, liquid soaps and lotions were not contaminated with germs. The personnel were eliminated as a potential source since its adherence in the National Campaign for Hand Hygiene was more than satisfactory. The use of broad spectrum antibiotics and the strategies applied by the Infectious Diseases Team of our Institute in the particular population of haematological patients were also considered: the same first-line antibiotics (such as piperacillin/tazobactam and cefepime) are still in use for the last 15 years and for the vast majority of patients with febrile neutropenia since the close surveillance of local epidemiology (that follows national epidemiology) allows their use. The multidrug-resistant *Pseudomonas aeruginosa* outbreak reminded us the importance of the following elements: the architecture of the hospital, the sanitary installations (including plumbing), the management of patient's excreta and the positive consequences of close interdisciplinary collaboration in crisis situations.

Discussion(ii)

The modern hospitals need space in order to separate clearly the clean from the dirty zones where material can be stored; in hospitals where storage space is scarce the clean material may be easily contaminated with waste and thus contaminate patients. The design of sanitary facilities is also taken into account: the splashing of water has to be avoided with sinks, tubs, showers and taps since the biofilm that occurs very rapidly in these installations will serve as a reservoir that will contaminate the users of poorly designed elements via the aerosols of water (18). Plumbing is primordial in the hospital setting where the biofilms will very quickly invade the limestone covering the pipelines serving to eliminate waste water. Pipelines have to be maintained as much cleanly as possible with recurrent scrubbing in order to assure proper drainage of waste water. Sharp angles and long horizontal lines promoting the stagnation of water are proscribed. The waste pipe leaks and blockages of pipe systems with backflow upstream and inundation are a major concern in old hospitals and have to be avoided by regular inspections, carefully thought repairs and education of users for a rational use of biodegradable paper (12).

Fig.1

Fig.5

Fig.2

Fig.3

Fig.4

Fig.6