

Management of GNR bacteremia in HCT: shifting patterns for outpatient antibiotic  
therapy in the modern era

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**Abstract**

Management of GNR bacteremia in HCT: shifting patterns for outpatient antibiotic therapy in the modern era

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Gram-negative rod bacteremia (GNRB) is a leading cause of morbidity and mortality in recipients of an allogeneic hematopoietic cell transplant (HCT). Treatment for these patients has historically occurred in the inpatient setting; however, shifts have been made towards outpatient care as it is associated with lower rates of hospital acquired infections (HAIs) and better use of hospital resources. Our objective was to identify clinical predictors at the time of GNRB diagnosis that would determine whether a patient spent a majority of their treatment days outpatient. Multivariate logistic regression analysis revealed that patients without severe gut graft vs. host disease (GVHD) (OR = 10.31, 95% CI = 4.89, 23.03), patients without neutropenia (OR = 8.96, 95% CI = 4.58, 18.42) and patients who received an outpatient GNRB diagnosis (OR = 8.59, 95% CI = 3.26, 27.22) were significantly more likely to receive greater than 50% of their antibiotic regimen in the outpatient setting. Further studies examining clinical predictors for outpatient care among GNRB patients are needed to better target antimicrobial stewardship, infection prevention and patient education interventions.

## Introduction

Gram-negative rod bacteremia (GNRB) is a leading cause of morbidity and mortality among allogeneic hematopoietic cell transplant (HCT) recipients<sup>1</sup>. Reported rates from prior studies of GNRB within HCT populations range from 17.3-34% of all bacteremia events<sup>1,2</sup>, but risk is dependent on the type of transplant, conditioning regimen and other post-transplant complications<sup>1</sup>. GNRB infections most frequently occur during periods of neutropenia or gastrointestinal graft-versus-host disease (GVHD), and are most often treated with parenteral antibiotics<sup>3</sup>. Risk factors for GNRB in these patients include prolonged neutropenia, intensive care unit (ICU) admission, age, GVHD and fluoroquinolone resistance<sup>1,4</sup>. Mortality has been shown to be adversely associated with delays in antibiotic therapy and incidence of multi-drug resistance (MDR) in this population, with mortality rates ranging from 17.9-50%<sup>1,2,5</sup>.

As inpatient intravenous (IV) therapies to treat high-risk patient populations are associated with substantial healthcare costs and increased risk for acquisition of MDR hospital-acquired infections (HAI), there has been an increasing effort to shift treatment of immunosuppressed patients with GNRB to outpatient departments<sup>6,7</sup>. One recent meta-analysis of 14 studies found no difference in efficacy between inpatient and outpatient management of cancer patients with febrile neutropenia<sup>7</sup>. Outpatient strategies may have the benefit of lower costs, decreased complications and reduction in rates of hospital-acquired multidrug-resistant organism (MDRO) colonization<sup>6,8</sup>. The delivery of outpatient parenteral antibiotics, administered by visiting nurses, family/caregivers or by patients themselves, is often made easier by choosing antibiotics with infrequent dosing schedules (e.g. once daily administration). In some cases, selecting an agent with more convenient dosing may result in less targeted/broader antibiotic therapy alternatives.

Outpatient antibiotic therapy is an enticing treatment option for this patient population; however, determining which patients are ideal candidates for outpatient care is challenging. A previous

study at our center identified annual trends in the incidence of GNRB among HCT recipients<sup>9</sup>, but no studies have examined the amount of outpatient therapy administered among HCT patients with GNRB. Our primary goal was to identify clinical risk factors at the time of GNRB diagnosis that may predict whether patients receive inpatient vs. outpatient care. In addition, we assessed shifts between inpatient and outpatient care over the study period, described the prevalence of MDROs among the most frequently cultured gram-negative rods (GNRs), and determined incidence rates of GNRB in this cohort.

## **Methods**

Study Population – Adult (>18 years) HCT recipients who received an allogeneic transplantation and treatment for GNRB at Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA) or University of Washington Medical Center (UWMC) from January 1, 2007 to December 31, 2016, were eligible for inclusion in the study. To be included in the study cohort, the patients needed a laboratory diagnosis of GNRB during the study period and needed to have received treatment during the first 100 days post-transplant; only the first episode of GNRB was included in these analyses. For subjects who have had multiple allogeneic transplants, only their first transplant at our study centers during the study period was included for analysis. Patients transplanted at outside hospitals were excluded from all analyses.

Study Design and Data Collection – We conducted a descriptive analysis within a cohort of HCT recipients with documented GNRB. In this study, we assessed changes in the proportion of time spent inpatient vs. outpatient among patients with GNRB. A retrospective cohort study was performed to identify clinical predictors at the time of GNRB diagnosis associated with whether a patient completed a majority of their 14-day therapeutic course within the inpatient or outpatient setting. Data were extracted from a center-maintained, prospectively-collected

database that includes information on demographic, laboratory, and clinical data from all HCT patients. Antibiotic resistance and use data were collected through UWMC laboratory medicine databases and supplemented by medical chart review. The FHCRC institutional review board approved this study.

Definitions – GNRB was defined as the isolation of any GNR organism from a blood culture. Early post-transplant GNRB events were excluded if the same organism was isolated within 14 days of a positive pre-transplant culture. Blood cultures positive for multiple GNR organisms in the same day were classified as a polymicrobial event, except when assessing resistance analyses<sup>9</sup>.

Inpatient vs. outpatient care was assessed during the standard 14-day therapy following the first positive blood culture. Counts of days spent inpatient vs. outpatient started 48 hours after the first positive GNR blood culture and ended at 14 days after the defined start. This was a conservative time frame to account for the delays associated with testing isolates for resistance prior to beginning targeted antibiotic therapy. A GNR MDRO was defined as a bacterium that had intermediate or full resistance to  $\geq 1$  agent in  $\geq 3$  of the following categories at the time of first culture: cephalosporins (cefepime, ceftriaxone, or ceftazime), anti-*Pseudomonas* beta-lactamase/beta-lactamase inhibitors, carbapenems, aminoglycosides, and fluoroquinolones. All *Stenotrophomonas maltophilia* isolates were considered MDRO<sup>4</sup>. Isolate resistance was defined according to the Clinical & Laboratory Standards Institute (CLSI) and categorized for the five most common GNRs identified within the cohort. Polymicrobial bacteremia events were considered MDR if any of the cultured organisms met criteria for MDR.

Statistical Analysis – For the descriptive analysis to assess changes in the proportion of time spent inpatient vs. outpatient among GNRB HCT patients, inpatient vs outpatient days were

calculated during the standard 14-day therapy starting 48 hours after the first positive blood culture for each patient. Proportion of treatment days spent outpatient were calculated in yearly and quarterly intervals over the study period and modeled by linear regression to assess for shifts.

For the primary analysis, a multivariate logistic regression was performed to identify clinical predictors at the time of GNRB diagnosis to determine if a patient completes a majority of their 14-day therapeutic course within the outpatient setting. The primary outcome was receiving greater than 50% of a patient's GNRB therapy in outpatient care. *A priori* selected predictors of interest included: underlying disease (e.g. acute myeloid leukemia, multiple myeloma, acute lymphoblastic leukemia, Non-Hodgkin lymphoma, myelodysplastic syndrome and other), severe gut GVHD grade  $\geq 2$  (yes / no), neutropenia  $\leq 500$  cells/ $\mu$ L (yes / no), conditioning regimen (myeloablative or nonmyeloablative), inpatient at the time of GNRB diagnosis (yes / no), polymicrobial bacterial culture (yes / no), and age at diagnosis ( $>65$  /  $\leq 65$ ).

Lastly, for the evaluation of GNRB incidence, we considered only the first GNRB event per patient. The incidence rates of GNRB during 100 days post-transplant were calculated in yearly intervals. Each patient contributed patient-days at risk from the day of transplant until GNRB, re-transplant, death or reaching 100 days, whichever occurred first. Changes in incidence rates over time were analyzed using a Poisson regression model with yearly time intervals as the independent variable and number of GNRB events as the dependent variable. All analyses were performed using RStudio (version 1.1.419).

## **Results**

Of the 2,165 transplants included in this cohort, 255 (11.8%) experienced at least one GNRB event during the first 100 days post-transplant. Among those who had a GNRB, the median age was 53 years (IQR: 43, 60) and the most prevalent underlying condition was acute myeloid leukemia (35.7%). Among these patients, neutropenia (33.3%) and severe gut GVHD (23.9%) were commonly observed, while polymicrobial bacteremia (9.8%) was less frequent (Table 1).

GNRB Incidence Rates – When considering only the first GNRB event per transplant, the overall incidence rate of GNRB was 1.31 events per 1000 patient-days (PD) (95% CI = 1.16, 1.48). Incidence rates varied over time, beginning at 1.50 events per 1000 PD in 2007 (95% CI = 1.02, 2.21), peaking at 1.95 events per 1000 PD in 2009 (95% CI = 1.42, 2.67), and declining to a low of 0.52 events per 1000 PD in 2014 (95% CI = 0.28, 0.98). Overall, the incidence rate of GNRB decreased from 2007 to 2016, although this trend was not statistically significant (Figure1).

Multivariable Analysis of Clinical Predictors – To study the association between clinical predictors at the time of GNRB diagnosis and outpatient therapy, we compared whether a patient received greater than 50% of their GNRB treatment in an outpatient setting to the presence of several risk factors. Adjusting for underlying disease, polymicrobial bacteremia, conditioning regimen and age, patients without severe gut GVHD (Odds Ratio [OR] = 10.31, 95% CI = 4.89, 23.03;  $P < .001$ ) and patients without neutropenia (OR = 8.96, 95% CI = 4.58, 18.42;  $P < .001$ ) were significantly more likely to receive greater than 50% of their antibiotic regimen outpatient. Additionally, receiving a GNRB diagnosis in the outpatient setting (OR = 8.59, 95% CI = 3.26, 27.22;  $P < .001$ ) was also associated with outpatient treatment.

Descriptive Analyses – When comparing the proportion of total outpatient days for this cohort by year, we see a statistically significant decrease in time spent outpatient over the study period ( $P$

<.01), peaking in 2010 with over 70% of all GNRB antibiotic treatment taking place in the outpatient setting. When analyzing the same data on the quarterly level, we also see a decreasing trend in time spent outpatient from 2007-2016; however, this trend was not statistically significant ( $P = 0.16$ ). We saw a decrease in the amount of time spent outpatient for GNRB over the study period, averaging 68% of treatment outpatient from 2007-2010 to 50% from 2011-2017 (Figure 2).

The five most common GNRs cultured from the bacteremia events were *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *S. maltophilia*, and *Escherichia cloacae* (Table 2). Excluding *S. maltophilia*, which was always classified as MDR by definition, *E. cloacae* had the highest rate of MDR at 23%. The overall rate of MDR among the remaining four pathogens was 20%.

## **Discussion**

In this large, single center retrospective cohort study, we identified predictors for outpatient antibiotic therapy among HCT recipients with GNRB over a 10-year period. GNRB was diagnosed in 11.8% of the adult allogeneic HCT population, with an overall incidence rate of 1.31 events per 1000 PD. We found that patients without GVHD or neutropenia and patients diagnosed with GNRB in the outpatient setting were statistically more likely to receive >50% of antibiotic therapy for GNRB in the ambulatory environment. In addition, although the amount of outpatient treatment days for GNRB patients varied over time, the proportion of time spent outpatient was 57% over the span of the study period, indicating a need to focus antimicrobial stewardship efforts on outpatient antibiotic therapy.

Other centers have identified risk factors for GNRB<sup>4,10</sup>; however, to our knowledge, no study has attempted to identify clinical factors at the time of GNRB diagnosis that would predict healthcare workers to preferentially use outpatient antibiotics. One of the challenges facing clinicians is determining which patients are ideal candidates for outpatient therapy given the complexity of their conditions<sup>11</sup>. Therefore, our data provides potential ways to identify patients for outpatient care.

Outpatient antibiotic therapy provides many benefits to both the patient and the hospital including improved patient satisfaction, reduction in the rates of nosocomial infections, and more effective use of hospital resources by increasing turnover and therefore bed availability<sup>8</sup>. Several groups have reported the response rates of outpatient antibiotic management ranging as high as 92.4 – 99% over the last 20 years<sup>12–14</sup>, but none have focused on such high-risk HCT recipients. The decrease in the total number of days of outpatient antibiotic therapy over time is interesting, particularly when taken into the context of shifts toward more outpatient management. With such low numbers of GNRB among our patients, those that do develop GNRB in the latter years may have additional risk factors for morbidity and mortality (e.g. increased age). Further investigation of such differences will be necessary in helping to understand physician decision-making regarding use of outpatient antibiotic therapy.

Nevertheless, at our center HCT recipients primarily have Hickman catheters placed for IV infusions, and tunneled catheters have been associated with lower rates of complications in comparison to peripherally inserted central catheters (PICCs)<sup>16</sup>. One study reported that 8% of their PICCs used in the outpatient setting suffered complications resulting in removal<sup>11</sup> as well as another finding that 71% of their readmission events were directly related to issues with outpatient services<sup>8</sup>. This provides an opportunity for infection control and antimicrobial stewardship teams to reduce the rates of these adverse events. Additionally, recent studies

have reported both an increase in self/caretaker administration of outpatient antibiotics along with no differences in rates of line infections between self-administered and clinic-based antibiotics.<sup>13,15</sup> With this shift towards more home-based outpatient care where there is no healthcare provider to administer antibiotics, a combination of enhanced training for patients and caregivers on self-care line management along with infectious disease consultation has the potential to reduce antibiotic administration complications<sup>11,17</sup>.

Our data demonstrates a lower prevalence of GNRB than what others have reported in similar HCT populations, where reported prevalence varies between 16 and 21%<sup>5,18,19</sup>. Rates of GNRB vary by study, most likely reflecting differences in antibiotic use, patient disease state, and length of follow-up post-transplant<sup>5,18,19</sup>. Although we observed an incidence rate of 1.31 events per 1000 PD, another study has reported rates as high as 2.39 events per 1000 PD.<sup>20</sup> Potential reasons for our lower rates include the implementation of central line bundles, chlorhexidine gluconate bathing, alcohol-impregnated line central catheter caps, as well as variations in antibiotic prescribing practices<sup>9</sup>. Differences between our findings and other prior studies may also be due to our definition of a GNRB event. Our follow up period was 100 days post-transplant and only included the first GNRB per patient, which may have led to an underrepresentation of GNRB at our center. Other studies tracked patients for up to 30 months<sup>5,21</sup>; however, the median time to first bloodstream infection was 48 days post-transplant, suggesting most events would be captured within the first 100 days<sup>5</sup>.

MDR GNRB pose an additional treatment risk due to the limited numbers of potential antibiotic choices. Unlike others' findings of MDRO rates among their GNRB patients ranging from 30 – 47%<sup>21–23</sup>, we observed a 20% MDRO rate among our five most common GNRs, excluding *S. maltophilia*. MDR rates vary by both region and center, with higher rates of carbapenem and fluoroquinolone resistance on the east coast of the United States<sup>24</sup>, which likely plays a role in

the differences in rates between our population and other previous studies. Potential strategies to reduce the rates of MDROs focus on infection prevention and antimicrobial stewardship interventions such as hand hygiene, proper contact precautions, reduction in use of invasive instruments, monitoring susceptibility patterns to identify optimal antibiotic choices<sup>25</sup>.

Our study has limitations commonly seen among retrospective cohort analyses. First, we were unable to attribute a decrease in GNRB rate to any one infection control intervention due to the consistently evolving management practices among the HCT transplant population. Such interventions take place in harmony with other changes in practice, therefore decoupling such changes to specific effects is not possible. Additionally, it is likely that variables linked to transplant practices changed over time and that other unmeasured confounders may have influenced our results. Furthermore, it is difficult to monitor antibiotic compliance of patients within the outpatient setting compared to inpatient, potentially leading to biased results. Finally, these results only reflect findings from a single center and may not be generalizable to other institutions as GNRB rates vary regionally<sup>5,18-20</sup>. The strengths of this study include 10 years of data with a large sample size of GNRB patients, which informs evidence-based decisions to improve outpatient antibiotic therapy.

In summary, GNRB rates at our center have declined overall while also seeing a decrease in outpatient treatment days during the latter stages of the study period. We hypothesize that this trend is in part due to the higher acuity of patients that our center has treated in more recent years. Therefore, most the GNRB events that we treat consist of our most complex patients who are often not ideal candidates for outpatient therapy. Further studies examining clinical predictors for outpatient care among GNRB patients are needed to better target antimicrobial stewardship, infection prevention and patient education interventions.

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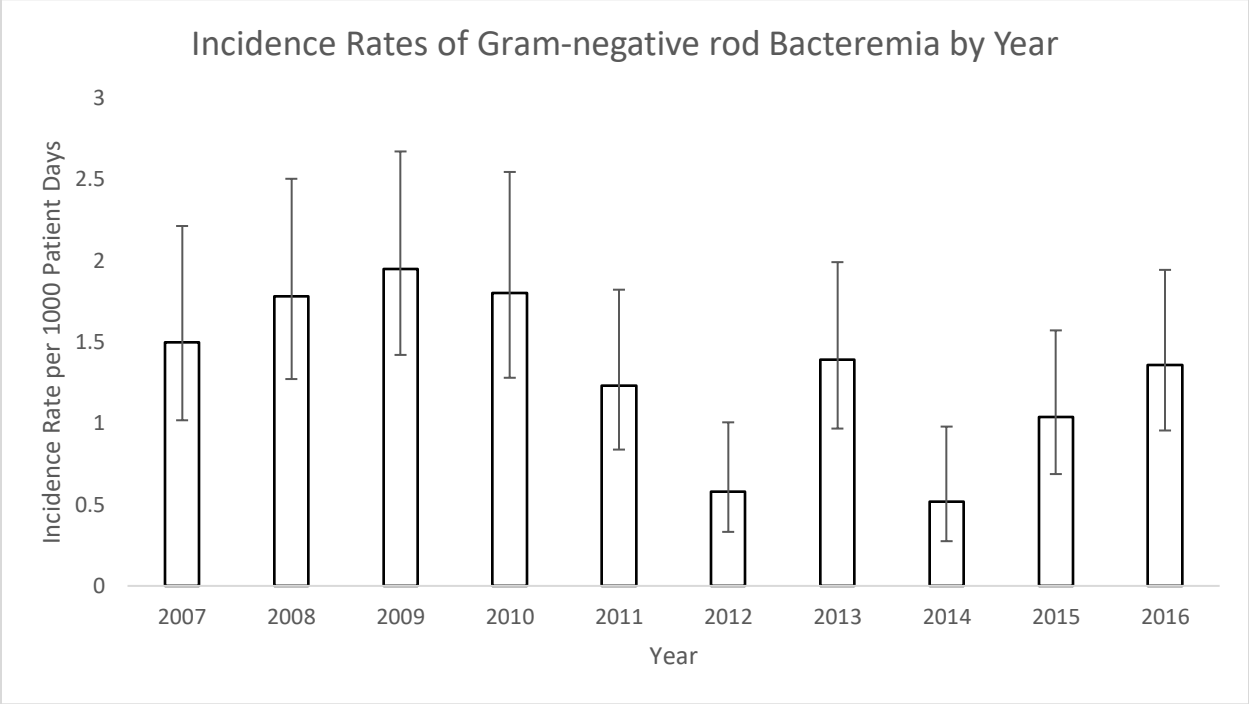
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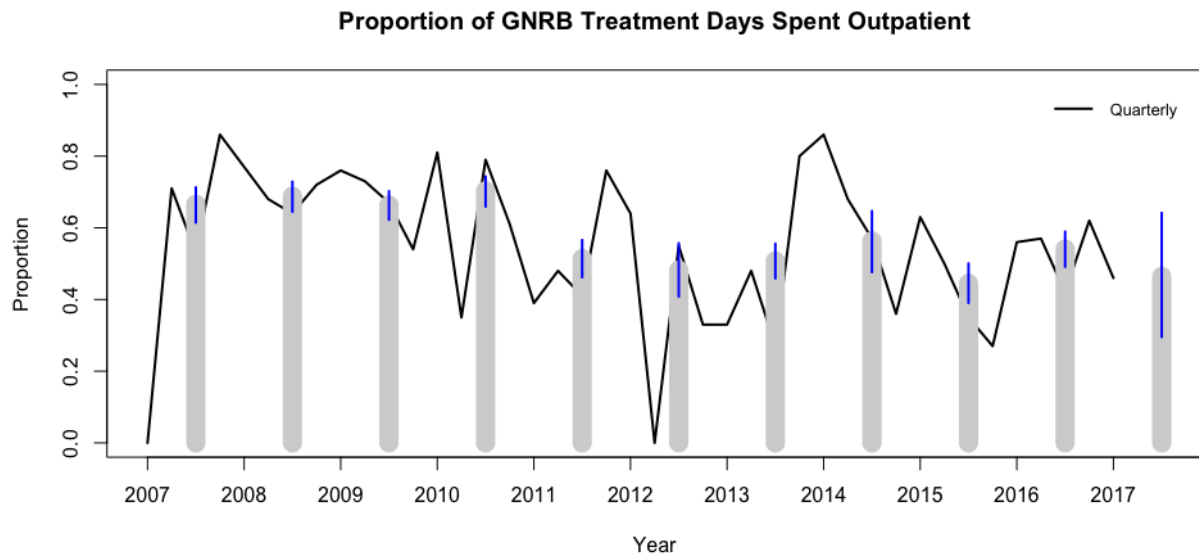
**Table 1:** Characteristics of adult allogeneic HCT recipients with lab-confirmed gram-negative rod bacteremia within 100 days post-transplant (n=255)

<b>Variables</b>	<b>n</b>	<b>%</b>
<b>Age (years) – median (IQR)</b>	53	(43, 60)
<b>Sex</b>		
Male	128	50.2
<b>Race/Ethnicity</b>		
Caucasian	183	71.8
Other	27	10.6
Hispanic	20	7.8
Asian/Pacific Islander	16	6.3
Black	9	3.5
<b>Underlying Disease</b>		
AML	91	35.7
MDS	44	17.3
ALL	40	15.7
Other	39	15.3
NHL	28	11.0
MM	13	5.1
<b>Severe Gut GVHD (<math>\geq</math> grade 2)</b>		
Yes	61	23.9
<b>Polymicrobial Bacteremia</b>		
Yes	25	9.8
<b>Conditioning Regimen</b>		
Myeloablative	98	38.4
<b>Neutropenia (&lt; 500 cells/<math>\mu</math>L)</b>		
Yes	85	33.3

Abbreviations: IQR-interquartile range; AML-acute myelogenous leukemia; MDS-myelodysplastic syndrome; ALL-acute lymphoblastic leukemia; NHL-non-Hodgkin's lymphoma; MM-multiple myeloma; GVHD-graft-versus-host disease



**Figure 1:** Incidence rate of first GNRB event, by year, 2007-2016



**Figure 2:** Proportion of treatment days spent outpatient by year (grey bars) and by quarter (black line), with 95% confidence intervals (blue lines)

**Table 2:** Five most common gram-negative rods isolated from blood cultures and percentage that were multi-drug resistant by year, 2007-2016

	All		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016	
	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>	n	%R <sup>m</sup>
<i>E. coli</i>	55	18.2	8	25	2	0	6	16.7	6	0	5	20	3	33.3	7	0	4	0	7	42.9	7	28.6
<i>K. pneumoniae</i>	31	16.1	2	0	6	16.7	5	20	4	25	1	0	3	0	4	25	0	--	3	33.3	3	0
<i>P. aeruginosa</i>	23	21.7	1	100	3	0	5	20	4	0	1	100	1	0	1	0	1	100	3	33.3	3	0
<i>S. maltophilia</i> *	19	100	3	100	1	100	3	100	3	100	2	100	2	100	2	100	3	100	0	--	0	--
<i>E. cloacae</i>	13	23.1	0	--	5	40	5	20	0	--	0	--	1	0	1	0	0	--	1	0	0	--

%R<sup>m</sup> Percent multi-drug resistant, \* all *S. maltophilia* cultures predetermined as multi-drug resistant by definition

