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REVIEW ARTICLE

Emerging bacteria in the new millennium

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INTRODUCTION

Infection remains a common complication in patients with hematologic malignancies, and despite significant advances in antimicrobial therapy and supportive care, is still associated with substantial morbidity and some mortality. The epidemiology of bacterial infection continues to change and is impacted upon by several factors, including the nature of the underlying immunological deficit(s), the nature of antineoplastic therapy, the use of chemoprophylaxis, the use of central venous catheters and other medical devices, and some local epidemiological factors. Constant surveillance and monitoring is necessary in order to detect epidemiological changes in a timely manner, and develop prevention/treatment strategies that take these epidemiologic changes into account. This review will focus on bacteria that are emerging as significant pathogens and are likely to cause therapeutic challenges in the near future, and the need for antimicrobial stewardship.

Bacterial infection: current spectrum

The current spectrum of bacterial infection in patients with hematologic malignancies is dominated by gram-positive bacteria, which cause between 45-75 percent of all bacterial infection in this patient subset (1-3). Unfortunately most databases focus only on monomicrobial bacteremic infections (where gram-positive organisms are predominant), and ignore or mention without specific detail infections at other sites (pneumonia, neutropenic enterocolitis, perirectal infections etc.) and polymicrobial infections (where gram-negative bacilli predominate), thereby painting an incomplete and inaccurate picture of the overall spectrum of bacterial infection. A major reason for this deficiency in information is the lack of consensus definitions for many infections, particularly in patients with severe neutropenia. Many organisms that are often innocuous in immunologically competent individuals and are often considered colonizers or contaminants (e.g. coagulase-negative staphylococci Corynebacterium spp.) are opportunistic pathogens in neutropenic patients (4,5). These issues highlight the need for developing standard criteria/definitions for describing infections in immunocompromised/ neutropenic patients, especially since the choice of antibiotic prophylaxis and/or empiric antibiotic therapy depends on accurate microbiological data.

Emerging bacteria

Emerging gram-positive organisms of concern are listed in table 1.

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Table 1. *Emerging gram-positive pathogens*

● Staphylococcus aureus
- community acquired MRSA (USA 300, USA 400)
- glycopeptide intermediate Staphylococcus aureus (GISA)
● Vancomycin-resistant (multidrug resistant) Enterococci
● Penicillin-resistant Streptococcus species
- Streptococcus pneumoniae
- viridans group streptococci
● Stomatococcus mucilaginosus
● Rhodococcus equi

Methicillin-resistant staphylococcus aureus (MRSA) have traditionally been associated with nosocomial infections. The incidence of MRSA infections worldwide has dramatically increased over the past 3 decades and MRSA now account for 60% of all S. aureus isolates admitted to the intensive care unit. Figure 1 depicts the increase in the frequency of MRSA at our institution over a 20 year period. Pulse field gel electrophoresis (PFGE) studies have demonstrated 8 distinct MRSA clusters (USA 100 – USA 800) of which USA 300 and USA 400 are predominantly from community acquired (CA– MRSA) (6). Recent epidemiological studies have demonstrated that these isolates have been introduced into the hospital environment from the community, and now account for 20% of nosocomial and 29% of healthcare associated blood stream infections (7). These CA-MRSA isolates frequently contain genes encoding for Panton-Valentine leukocidine (PVL), a leucocyte killing exotoxin linked to the development of cutaneous abscesses and severe necrotic infections, and are presenting clinicians with new therapeutic and infection control challenges. Staphylococcal isolates are classified according to vancomycin susceptibility breakpoints into susceptible (MIC≤ 4.0μg/ml), intermediate (MIC>4.0 but <32.0μg/ml) and resistant (MIC≥32.0μg/ml). There are disturbing reports of relatively large outbreaks of GISA (glycopeptide intermediate *S.* aureus) infections, which have required extraordinary measures to control (8). What impact these (and truly vancomycin-resistant) isolates will have on neutropenic/immunosuppressed patients remains to be seen, particularly in an area of limited therapeutic options.

Vancomycin-resistant enterococci (VRE) which are often multi-drug resistant are the third most common gram-positive pathogens isolated from neutropenic patients (9). These organisms frequently colonize the intestinal tract particularly in patients with hematologic malignancies and recipients of stem cell transplantation (10). Approximately 30% of high-risk patients with fecal colonization by VRE develop a subsequent systemic infection (positive predictive value-29.3%), whereas virtually no one without VRE fecal colonization develop a systemic infection (negative predictive value, 99.9%). Figure 2 shows the frequency of VRE isolates at our institution over a 15 year period. These isolates are associated with greater morbidity and mortality than susceptible enterococcal isolates, and of concern are reports of emerging resistance to agents such as linezolid (11).

Stomatococcus mucilaginosus can colonize the oro-pharynx and are being isolated from blood culture specimens of neutropenic patients with increasing frequency, particularly in that subset of patients who develop severe chemotherapy induced oral mucositis. Disseminated infection including meningitis can occur in up to 50% of cases, and is associated with substantial morbidity and mortality (12). Streptococcus species including *S.* pneummoniae and viridans group streptococci are becoming increasingly resistant to penicillin and are associated with invasive disease (13,14). Rhodococcus equi cause pulmonary infections in patients with HIV-AIDS, but cause catheter-related bacteremias more often in neutropenic cancer patients (15). Many of these organisms are being identified more frequently as new sophisticated laboratory techniques such as 16s ribosomal typing become widely available.

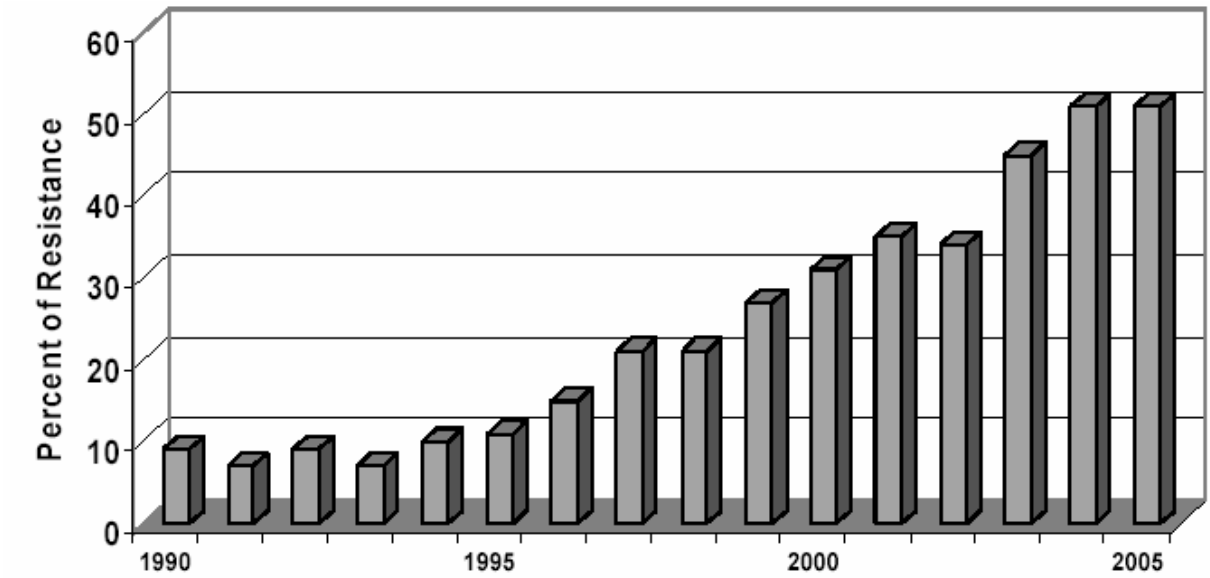

Figure 1. *Frequency of MRSA (methicillin-resistant S. aureus) at MDACC, 1990-2005 (*Data from cumulative susceptibility report section of Microbiology Lgraviss, IC Department, May 2006*)*

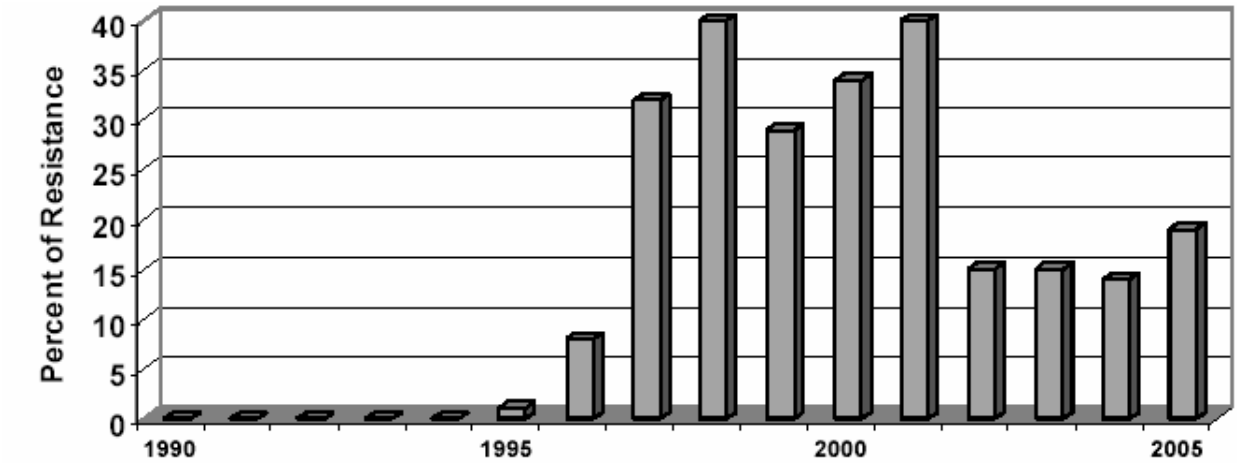

Figure 2. *Frequency of VRE (vancomycin-resistant enterococci) at MDACC, 1990-2005 (*Data from Cumulative Susceptibility Report Section of Microbiology Lgraviss, IC Department, May 2006*)*

Emerging gram-negative pathogens are listed in table 2. Non-fermentative gram-negative bacilli (NFGNB) have emerged as important pathogens in neutropenic patients over the past decade and cause up to 50% of all gram-negative infections in such patients (16). In two position papers entitled "Bad Bugs No Drugs", and "Bad Bugs Need Drugs" the Infectious Diseases Society of America (IDSA) has identified several NFGNB as organisms of concern and stressed the need for new drug development to combat them (17,18).

Acinetobacter species are commonly found in the environment, can cause bacteremia, pneumonia (especially ventilator assisted pneumonia), and supurative infection of virtually any organ system, with reported mortality rates ranging from 19% to 54%. Increasing resistance due to multiple mechanisms including aminoglycoside modifying enzymes, ESBL production, carbapenemases, and changes in outer membrane proteins and penicillin binding proteins, have made therapy a challenge (19,20).

Table 2. *Emerging gram-negative pathogens*

● Non-fermentative, gram-negative bacilli
Acinetobacter baumannii
Alcaligenes spp./Achromobacter spp.
Pseudomonas aeruginosa (multidrug resistant strains)
Stenotrophomonas maltophilia
● Enterobacteriaceae
ESBL* producing *E. coli* and *Klebsiella* spp.
Quinolone resistant *E. coli*

* ESBL:Extended spectrum beta-lactamase

Similar, but less common are Achromobacter/Alcaligenes species which are also often multidrug resistant (21). Recent experience from our institution indicates that these organisms caused infections more often in patients with hematologic malignancies than those with solid tumors (67% vs 33%). Catheter-related or unrelated bacteremias, pneumonias, and urinary tract infections were common. Resistance to aminoglycosides, cephalosporins, monobactams, and quinlones was widespread. Only the carbapenems and TMP/SMX had reliable in-vitro activity against these organisms (21).

Pseudomonas aeruginosa has always been among the three most common gram-negative pathogens to be isolated from neutropenic patient (22). These organisms have now acquired multiple mechanisms of resistance, which render all currently available antimicrobial agents inactive against them (23,24). Drugs previously abandoned from clinical practice due to unacceptable toxicity (colistin, polymyxin B) appear to have the most reliable in-vitro activity against these organisms, but have a dismal therapeutic record in neutropenic patients (25).

Stenotrophomonas maltophilia have emerged as important pathogens in cancer patients, particularly among patients who have received prolonged therapy with carbapenems and other broad-spectrum agents (26). Bacteremia, pneumonia, and complicated urinary tract infections occur most often. Trimethoprim/sulfamethoxazole is the agent of choice, but increasing levels of resistance are being documented. Tigecycline, a novel minocycline derivative, appears to have reliable activity against S.maltophilia, but clinical study particularly in neutropenic patients, is lacking.

Of all aerobic, gram-negative bacilli, E. coli and Klebsiella spp. are the most frequent pathogens in neutropenic, cancer patients. Common infections include bacteremia, pneumonia, urinary tract infection, and other nosocomial infections. These organisms have been reported to produce extended spectrum beta-lactamases with varying frequency from all parts of the globe (27). ESBL's render aminopenicillins, extended spectrum cephalosporins, ureidopenicillins, and to some extent even carbapenems, inactive. Resistance to other classes of antimicrobials (aminoglycosides, quinolones, TMP/SMX) is common among ESBL producing organisms. Currently, the carbapenems and tigecycline appear to be the most active agents against ESBL producing gram-negative bacilli.

Excessive quinolone usage (particularly for chemoprophylaxis in patients with hematologic malignancies) has been associated with the emergence of quinolone-resistant (often multidrug resistant) E. coli. These organisms are associated with bacteremia and disseminated infections, and greater morbidity and mortality than quinolone susceptible isolates (personal observations).

Recent data from the MYSTIC database has shown that at some cancer centers with high-volume quinolone usage, quinolone resistance rate among E. coli are in the range of 70-80% (unpublished data). These data are of great concern, and mandate a fresh look at the indications for chemoprophylaxis.

Quinolone usage has also been associated with the emergence of strains of Clostridium difficile that are hyperproducers of Toxins A and B, (table 3) (28). Additionally, with the increasing usage of purine analogs (e.g. fludarabine), monoclonal antibodies (ritumximab, alemtuzumab) and Tumor Necrosis Factor-α Antagonists (infliximab),

organisms not usually associated with neutropenia are emerging as significant pathogens (table 3). These include Mycobacterium tuberculosis and other mycobacteria, Listeria monocytogenes, and Nocardia species (29). These organisms need to be taken into account when choosing regimens for empiric therapy when patients who have received these agents develop neutropenic fever.

Table 3. Other *emerging bacterial pathogens*

● Clostridium difficile (strains that hyperproduce toxins A and B)*
● Mycobacterium tuberculosis and other mycobacteria†
● Nocardia species†
● Listeria monocytogenes †

* associated with fluroquinolones usage

† associated with infliximab usage, purine analong and monoclonal antibody (rituximab, alemtuzumab) usage

SUMMARY

The spectrum of bacterial infection in patients with hematologic malignancies continues to change. The past decade has seen the emergence of several multidrug resistant bacterial pathogens, most of which have occurred due to selection pressures exerted by heavy antimicrobial usage. Global trends as well as local epidemiologic patterns need to be taken into consideration when devising prophylactic/therapeutic strategies for these high-risk patients. Unfortunately, the pipeline for the development of novel antimicrobial agents is relatively dry. The judicious use of currently available agents, strict adherence to infection control policies and procedures, and hopefully the development of novel antineoplastic therapies that do not cause myelo-/immuno-suppression, are strategies that will help meet some of these challenges in the years to come. These strategies, when used in combination are referred to as antimicrobial stewardship (30). Various strategies have been used, and none has been proven to be the strategy of choice (table 4). These include "front end" approaches such as "antibiotic cycling", "antibiotic heterogeneity", and restricted formularies. Other strategies are referred to as "back end", approaches, such as "streamlining" or "de-escalation", after microbiological data have become available. Perhaps a combination of both front-end and back-end strategies will be needed to produce optimal therapeutic effects, yet limit toxicity and the emergence of resistant organisms. Antimicrobial stewardship is best accomplished by creating an institutional program or team whenever resources permit (30,31).

Table 4. Various strategies for antimicrobial stewardship

● Education
● Formulary restriction with pre-authorization requirements
● Guidelines and clinical pathways using antimicrobial order forms
● Streamlining or de-escalation
● Dose/duration optimization
● Antimicrobial cycling or rotation
● Antimicrobial heterogeneity with feedback and intervention
● Oral conversion and early discharge

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