

Blood Stream Infections in Patients with Febrile Neutropenia

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Introduction

- Bacteremia is still a relatively common complication in patients with febrile neutropenia (FN) as evidenced by a recent paper by Viscoli et al. (2006) in a large cooperative group trial where 29% (approximately equal proportions of Gram-positive and Gram-negative pathogens) of cases were bacteremic.
- Elting et al in 1998 showed mortality is increased in FN with bacteremia, especially when a clinical site of infection is present (complex bacteremia)

Introduction (cont.)

- In previous EORTC-IDG (IATG) published studies the incidence of bacteremia varied between 32% in 1973 to 22% in 1994.
- During the same time period, the proportion of Gram-positive pathogens increased. The proportion of bacteremia caused by Gram-negative and Gram-positive changed from 71% and 29% (1973-1978) to 33% and 67% (1992-1994) respectively

Introduction (cont.)

- The explanation for the change in the pathogens causing bacteremia and also non-bacteremic documented infections is thought to mainly be a result of prophylaxis with cotrimoxazole and fluoroquinolones and probably also due to the increased use of central lines in these patients
- More mucositis and use of antacids may also contribute
- Gram–negative pathogens are reduced with quinolone prophylaxis but the complications and death rates are not significantly changed

Introduction (cont.)

- Gram-negative infections (especially bacteremia) generally have a higher mortality than those due to Gram-positive bacteria.
- Although Gram-negative pathogens may be decreasing in most developed countries the proportion recently (2001-2005) seen in FN in developing countries such as Malaysia, Lebanon etc. remains high, perhaps related to less use of quinolone prophylaxis and central lines, due to their high cost

Introduction (cont)

- The main Gram-negative pathogens causing Gram-negative bacteremia continue to be *Escherichia coli*, *klebsiella species*, and *Pseudomonas aeruginosa*, although others are being seen with increasing frequency
- Coagulase-negative staphylococci remain the most frequent cause of Gram-positive bacteremia but others are also seen

Recent Series-Klastersky

- Klastersky et al (IJAA 2007) have recently updated this subject, while describing data on bacteremia from a MASCC study used to produce their validated Risk Index
- The purpose of their study was to try to identify factors predictive of bacteremia in FN to tailor empirical antibiotic therapy to cover the increased risk of this situation

Recent series (cont.)-Klastersky

- Their study combined hematological and solid tumor patients, although most of the data came from hematological patients especially SC transplants
- The patients on this study came from 2 International observational studies (1139 collected from 1994-1997 and 1003 from 1997-2005) were pooled (2142 patients)

Recent Series (cont)-Klastersky

- Klastersky found that 1643 (77%) of the patients studied did not have bacteremia and 57 (2.9%) died, while among the 499 with bacteremia 49 (10%) died.
- A higher proportion of patients who had bacteremia also had a higher rate of non-lethal complications (21% versus 13%) in patients with hematological malignancies
- Similar differences occurred in patients with solid tumors (22% versus 8%)

Recent Series (cont.)-Klastersky

- The proportion of hematological malignancies was higher (2.7 versus 1) in patients with bacteremia ($p < 0.001$)
- Patients with a clinical site of infection (complex bacteremias) had a higher mortality rate among patients with bacteremia (12% versus 8%) than in those without it ($p = 0.07$).

Recent Series (cont.)-Klastersky

- The mortality rates were 4% and 3% in non bacteremic patients with hematological malignancies or solid tumors respectively
- The figures were 5 and 13% in bacteremic cases ($p < 0.001$) for both cancer categories
- Among hematological patients, those with BMT patients had a lower mortality (3%) than patients on other treatments (6%) ($P = 0.04$)

Recent Series (cont.)-Klastersky

- 168 bacteremias were caused by single Gram-negative organisms with an 18% mortality rate.
- *E coli*, *Klebsiella sp.* and *Pseudomonas aeruginosa* occurred frequently enough as a cause of bacteremia for a meaningful analysis, with respective death rates of 18%, 10% and 31%

Recent Series (cont.)-Klastersky

- Coagulase-negative staphylococci caused 50% of the single Gram-positive bacteremias with a mortality rate of 6%
- There were 73 Streptococcal bacteremias with a 4% mortality rate
- There were 48 polymicrobial bacteremias with a 13% mortality rate (all but one with a mixture of Gram-positive and Gram-negative or multiple Gram-negative pathogens)

Recent Series (cont.)-Klastersky

- Use of prophylactic antibiotics was associated with less frequent Gram-negative than Gram-positive bacteremia (25% vs. 75% ($P < 0.001$)).
- In patients with no antibiotic prophylaxis, it was almost equal (52% vs. 48%)
- Granulopoiesis stimulating factors did not significantly affect the type of bacteremia but only a minority of patients received them, while most patients received prophylactic antibiotics.

Recent Series (cont.)-Klastersky

- There did not appear to be any relationship between the outcome (complications or mortality) of a single organism Gram-positive or Gram-negative bacteremia and whether or not the patient received either prophylactic antibiotics or granulopoiesis stimulating agents.
- Mortality was still higher in Gram-negative bacteremia

Recent series (cont.)-Klastersky

- The most common severe complications overall were hypotension and confused/altered mental status (30-60%)
- Respiratory and Renal failure were also relatively common complications. (8-40%)
- The complications did not occur with different frequencies with the presence or absence of bacteremia or by the pathogen identified

MASCC Risk Model

For each of the following characteristics present at onset of the febrile episode, the patients receive the corresponding points :

| <u>Characteristic</u> | <u>Points</u> |
|---|---------------|
| Burden of illness | |
| No or mild symptoms | 5 |
| Moderate symptoms | 3 |
| No hypotension | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or no previous infection in hematological tumor | 4 |

MASCC Risk Model Cont'd

| <u>Characteristic</u> | <u>Points</u> |
|-----------------------|---------------|
| Outpatient status | 3 |
| No dehydration | 3 |
| Age < 60 years | 2 |

The overall score is obtained by summing the individual points (points for burden of illness are not cumulative). The maximal score is 26 points.

Patients with a score ≥ 21 are considered by the rule as being at low-risk for serious complication.

Comparison of Talcott's and MASCC rules – Validation set (n=383)

| | <u>Talcott</u> | <u>MASCC</u> |
|-------------------------------|----------------|--------------|
| Patients at low risk | 26% | 63% |
| Positive predictive value | 93% | 91% |
| Negative predictive value | 23% | 36% |
| Specificity | 90% | 68% |
| Sensitivity | 30% | 71% |
| Global misclassification rate | 59% | 30% |
| Deaths in low-risk patients | 3 (3%) | 4 (1.6%) |

Recent Series (cont.)-Klastersky

- Complications occurred more frequently when patients had MASCC scores <15 compared to those with MASCC scores of 15-20
- In the 451 patients with both single Gram-positive and Gram-negative bacteremia, there was a significant difference in the frequency of overall complications and mortality between patients with MASCC scores of <21 or >21 ($P<0.01$)

Recent Series (cont.)-Klastersky

- In all bacteremic patients (499), the rate of overall complications and death were 18% and 3% respectively, while they were 49% and 19% in the 209 patients with a MASCC score <21 (both p values <0.001)
- In patients with Gram-negative bacteremia and a MASCC score <15 , the non-lethal complication rate and death rate were 39% and 43% respectively.
- With Gram-positive bacteremia and a MASCC score of <15 , the non-lethal complication rate was 50% and the mortality was 28%.

Recent Series (cont.)- Kanafani

- This study by Kanafani et al (IJID 2007) included 177 episodes of FN (from a 400 bed teaching Hospital in Lebanon) seen between January 2001 and December 2003
- Blood cultures were positive in 33 episodes (18.6%), which was lower than previously (30% in 1999 and 28.8% in 1995-1998)

Recent Series (cont.)-Kanafani

- The ratio of Gram-negative to Gram-Positive bacteremias was 2.4:1 (26/33 episodes were Gram-negative) in the recent study, while it was 1.5:1 and 1.8:1 from 1995-1998 and 1999 respectively, so Gram-negative bacteremia is increasing, by comparison to the Klustersky series, which suggests it is now less common.
- However the same Gram-negative and Gram-positive pathogens predominated.

Recent Series (cont.)-Kanafani

- In the recent study, there were 5 polymicrobial bacteremias, which were not seen previously
- Many details on outcome were not available but 7.5% of all episodes of FN were fatal
- The in hospital mortality was 12.1% compared to 20% in the previous periods
- The explanation for the high incidence of Gram-negative pathogens is the infrequent use of central catheters and prophylactic antibiotics in this Developing country

Recent Series (cont.)-Baskaran

- This retrospective study by Baskaran et al (IJID 2007) of all patients with FN at 1 center took place between January 1/2004 and January 31/2005 in Kajang Malaysia
- 116/120 episodes were seen in 67 patients.
- 50 episodes (43.1%) in 37 patients had documented bacteremia
- 35 episodes had single organisms on blood culture, while 10 episodes had 2 isolated pathogens and the remaining 5 had 3 or more isolated pathogens

Recent Series (cont.)-Baskaran

- The same Gram-negative pathogens predominate but *Enterobacter species* made up 6.8% which was slightly higher than *Pseudomonas aeruginosa* (5.5%)
- Coagulase-negative staphylococci were the predominant Gram-positive pathogen (23.3%)

Recent Series (cont.)-Baskaran

- Thirteen patients received antibiotic prophylaxis (5 were bacteremic)
- 4/5 were resistant to the prophylactic antibiotics used.
- Line-related infections accounted for 23.3% of the total source for FN
- Of the 12 line infections that were associated with bacteremia, only 4 yielded Gram-positive pathogens alone but 3 were mixed

Recent Series (cont.)-Baskaran

- This study also emphasizes the difference in the pathogens seen in Partially Developed or Developing countries, with a much greater frequency of Gram-negative pathogens as the pathogens seen with FN including bacteremias

Markers to Predict Bacteremia in FN

- Vekemans et al (CID 2007) looked at low Mannose-Binding Lectin (MBL) concentration in patients with hematological cancer to see if it was associated with severe infections
- MBL is a serum protein important in innate immunity. It initiates the complement cascade through the binding of the cellular membrane constituent sugars present on the surface of pathogens.

Markers to Predict Bacteremia in FN (cont.)

- The concept is that patients with hematological cancer on chemotherapy who are MBL-deficient have a higher risk of developing infectious complications than do non-MBL-deficient patients.
- The major (primary) end point of this study was the ratio of the duration of FN to the total duration of neutropenia

Markers to Predict Bacteremia in FN (cont.)

- There were 255 eligible patients who had MBL plasma concentrations determined on day 1 of chemotherapy or during the 3 days preceding chemotherapy.
- 62 (24%) of the patients were MBL-deficient
- The primary end point was similar in the 2 groups (MBL and non-MBL-deficient)

Markers to Predict Bacteremia in FN (cont.)

- The number of severe infections was higher in the MBL-deficient group
- The severe infections developed earlier in this group.
- Multivariate analysis was done to correct for other factors that might increase the rate of severe infections.

Markers to Predict Bacteremia in FN (cont.)

- When acute leukemia patients were eliminated, the rate of severe infection was higher in MBL-deficient patients ($p < .05$)
- The time to first severe infection during neutropenia was shorter in MBL-deficient patients (10 vs. 21 days; $P = .05$)
- In those patients (165) without leukemia (44 MBL-deficient) the time to severe infection was shorter in MBL-deficient patients (8 vs. 35 days; $P = .01$)

Markers to Predict Bacteremia in FN (cont.)

- In this data set there was also information on bacteremias.

The univariate RR for Septicemia/100 days was 2.0 for patients who are MBL-deficient as compared to those that are not MBL-deficient.

- This was the highest RR found in the study
- Bacteremia also developed earlier in the MBL-deficient group ($p = .02$)

Markers to Predict Bacteremia in FN (cont.)

- Schlapbach et al (Pediatr Blood Cancer 2007) looked at MBL concentrations in a neutropenic pediatric population.
- They looked at 177 FN episodes in 94 patients.
- They observed more frequent episodes of FN in both children with very low and normal MBL concentrations but those with very low levels were more likely to develop bacteremia (RR 2.62 but this result was not statistically significant) which does possibly support the concept that MBL may be a useful marker for severe infection (?bacteremia)

Markers to Predict Bacteremia in FN (cont.)

- Other laboratory markers such as IL-6, IL-8 and Procalcitonin have also been used and are likely superior to C-Reactive Protein (Kern-CID-2006)
- IL-8 seems to be very specific in some studies and a low level at fever onset may virtually eliminate the possibility of Gram-negative bacteremia and low levels of Procalcitonin (0.5ng/mL) may also help in predicting bacteremia

Testing to Predict Bacteremia in FN (cont.)

- These markers need further testing and may be useful to fine tune the predictive value of the MASCC score both to predict the general risk of developing FN and more particularly bacteremia (especially when caused by Gram- negative pathogens)
- However, they are not yet ready for routine use

Conclusions

- Bacteremia still remains frequent (30%) in patients with FN
- Although Gram-positive pathogens are clearly more frequently seen in Developed countries, this may not be the case in Developing countries and Gram-negatives may be making a “comeback” everywhere

Conclusions (cont.)

- The increase in Gram-positive pathogens may be due to the increased use of prophylactic antibiotics (especially quinolones) and the increased placement of central lines in Developed countries
- Gram-negative bacteremia (especially Complex) has a higher mortality rate

Conclusions (cont.)

- Polymicrobial bacteremias are getting more frequent and may increase the mortality rate
- The same pathogens (*E.coli*, *Klebsiella sp*, *Pseudomonas aeruginosa* and coagulase-negative staphylococci still predominate
- Lower MASCC scores (<15) predict for severity of infection and help to predict the likelihood of developing a bacteremia with a higher death rate

Conclusions (cont.)

- Other laboratory markers, especially low levels of IL-8 and Procalcitonin may be good negative predictors for FN and bacteremia
- Perhaps these tests should be combined with Risk scores such as MASCC to fine tune our ability to predict for serious infections, particularly bacteremia
- More research is required to improve our approach to blood stream infections in patients with FN