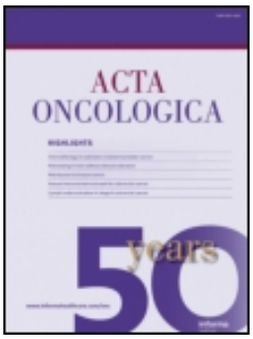

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REVIEW ARTICLE

The Norwegian experience with penicillin G plus an aminoglycoside as initial empiric therapy in febrile neutropenia; a review

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Abstract

Background. The occurrence of antibiotic resistance and the use of broad-spectrum antibiotics are relatively low in Norway. The national recommendation in febrile neutropenia (FN) is prompt initial therapy with penicillin G plus an aminoglycoside. We sought to evaluate the evidence behind this recommendation. *Methods.* We did a literature search in Medline and EMBASE with search terms penicillin, aminoglycoside and febrile neutropenia. *Results.* Seven Norwegian studies (six adult and one pediatric) conducted over the last 25 years were identified. They all conclude that penicillin G plus an aminoglycoside are effective and safe initial empiric antibiotic therapy in FN provided the regimen is modified if the clinical response is unsatisfactory. Overall 40–50% of the patients required only penicillin G and an aminoglycoside during their FN episode. The overall fatality rate was similar in the Norwegian and in international studies. *Conclusion.* Many countries use a broad-spectrum β-lactam as initial therapy in FN. International experts are sceptic towards the Norwegian recommendations. We discuss the arguments for and against penicillin G plus an aminoglycoside in FN. The main arguments to continue the Norwegian treatment tradition are the satisfactory clinical results and the reason to believe that it contributes to the low levels of antibiotic resistance in Norway.

Antibiotic use and microbiological epidemiology

The tradition in Norway has been to be restrictive with regards to implementing new broad-spectrum antibiotics. The clinical bacterial isolates have remained relatively sensitive compared to clinical bacterial isolates in many other countries and regions of the world. The general recommendations in Norwegian hospitals [1] are to use a combination of penicillin G and an aminoglycoside as empiric therapy in sepsis of unknown origin, as well as in febrile neutropenia (FN). Further recommendations are in short to use penicillin G or V in lower respiratory tract infections, to use aminoglycosides, mecillinam or trimethoprim as empiric therapy in urinary tract infections, and to use penicillinase-stable penicillins or penicillin G or V in simple skin and wound infections.

The national Norwegian NORM review [2] found stable microbiological sensitivity trends and stable antibiotic consumptions in 2010, compared to previous years. For example, there were only 10 blood culture isolates (1.0%) of MRSA among 1005 *Staphylococcus aureus* blood culture isolates. Vancomycin-resistant enterococci (VRE) were virtually absent (one isolate). *Streptocoocus pneumoniae* in blood culture and cerebrospinal fluid isolates with decreased sensitivity to penicillin G was 3.0% (22 of 730). Three isolates also showed decreased sensitivity to cephalosporins. *Escherichia coli* and klebsiella species blood culture isolates were mainly sensitive to all broad-spectrum β-lactams. Of *E. coli*, 5.2% were resistant to gentamicin. This is an increase from 4.0% in 2009. Ciprofloxacin is the only fluoroquinolone used in large scale in Norway. There was a significant increase in resistance to ciprofloxacin in *E. coli* from 3.3% to 8.6% in 2009. In 2010 the degree of resistance was reduced to 7.7%; the numbers are, however, adjusted according to new cut-off sensitivity

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limits. Altogether, the ciprofloxacin resistance is disturbing. Extended-spectrum-β-lactamase (ESBL)-producing *E. coli* and klebsiella isolates are present at low levels (2.6%), and they are closely monitored.

Our opinion is that the pattern of antibiotic use is a main contributor to the low levels of antibiotic resistance. We even think that the total use of antibiotics and the amount of broad-spectrum antibiotics in particular, can be further reduced [3].

Norwegian studies of penicillin G plus an aminoglycoside in FN

A literature search in Medline and EMBASE was unable to identify other clinical studies of penicillin G and an aminoglycoside than the seven Norwegian studies presented here. Experts in the field are not aware of any other relevant studies. Another prospective, randomized, controlled trial, comparing penicillin G and an aminoglycoside with meropenem in lymphoma and leukemia patients with FN, was closed with 323 randomized patients 1 November 2011. The prospected number of randomizations was 300 (EudraCT number: 2005-004211-30). However, no interim analysis was allowed. The study will now be monitored and analyzed before publication.

The first Norwegian FN trial was a prospective randomized controlled trial performed at one of the major hematological centres in Norway in the 1980s. It was presented at the 1989 Glaxo Ceftazidime Symposium at Gol in Norway [4], but unfortunately, it was never published in a peer-reviewed journal. The study asked if ceftazidime is at least as effective and safe as the combination of penicillin G and netilmicin, which was then the standard treatment in FN. Addition of cloxacillin and/or metronidazol was allowed. One hundred and sixteen episodes were evaluable. Ninety six percent of the patients in the ceftazidime arm and 89% in the penicillin G and netilmicin arm were successfully treated (Table I). The difference between the groups was not statistically significant. The six patients who did not survive, died secondarily to their underlying malignancy and not due to infection.

Two retrospective FN studies were published in 1998 and 1999 [5,6]. Both studies evaluated patients with acute leukemia. Hammerstrøm et al. [5] looked into 84 episodes of documented bacteremia. Of the isolates, 54% were Gram-negative rods. Penicillin G and an aminoglycoside were given in 43% of the episodes. Only 15% of the patients had an infection with an isolate sensitive to penicillin G. All the Gram-negative isolates were sensitive to tobramycin, and 52% of the Gram-positive isolates were sensitive to penicillin G (Table II). No patient died secondarily to the initial bacteremia.

Tangen et al. [6] examined 276 episodes of FN in 85 patients. Penicillin G and an aminoglycoside were given in 72% of the episodes, and 94% of these episodes had a successful outcome. Modifications of the penicillin G and aminoglycoside regimen occurred in 69% of the patients who received penicillin G and aminoglycoside. Unless they experienced complications during the FN episode, they were considered successful (Table I). Both these studies concluded that penicillin G and an aminoglycoside appeared to be an efficient and safe initial empiric therapy in FN, provided the initial regimen was modified if the clinical response was not satisfactory. Hammerstrøm et al. [7] presented a followed up study on the microbiological bacterial epidemiology of hematological patients at the same center from 1995 until 2005. He did not find any changes calling for a new antibiotic policy [2,7]. Therefore, the results from these initial studies are still considered an adequate base for the guidelines of the initial empiric antibiotic treatment in FN.

Sigurdardottir et al. [8] observed prospectively 282 episodes of FN in 243 patients, of whom the majority had a hematological malignancy (the exact number was not presented). The microbiological epidemiology related to therapy with penicillin G and an aminoglycoside was the main focus of this study (Table II). Bacteremia was documented in 34% of the episodes. The most common isolates were *E. coli* (26% of the culture-positive cases) and α- and non-hemolytic streptococci (16%). All the Gram-negative isolates were sensitive to gentamicin, ceftazidime and ciprofloxacin. All the streptococci were sensitive to penicillin G. Of the Gram-positive isolates, 63% was sensitive to penicillin G. Penicillin G and an aminoglycoside were administered in 59% of the episodes. There were five isolates of Pseudomonas species, and four of these episodes were successfully treated with initial penicillin G and an aminoglycoside (personal communication). The overall fatality rate was 7% whilst 1% of the patients with bacteremia died.

The only prospective randomized controlled multicentre trial was published in 2007 [9]. Tobramycin once daily was compared to tobramycin three times daily, both given with penicillin G to FN cancer patients. When the study was started in 2001, aminoglycosides were regularily given once daily in most clinical situations. In a few clinical settings, including FN, the three times daily regimen was still considered optimal. One hundred and seventy-four patients were evaluable. Of these, 155 patients had lymphoma or leukemia. In both arms of the study, 40% of the patients had no modification of the antibiotic regimen; which was the primary endpoint. Adjustments of the tobramycin dose and addition of

Table I. Clinical response comparison of the Norwegian febrile neutropenia studies with penicillin G and an aminoglycoside.

Study (first author) Year of publication	Type of study	Underlying malignancies	Patients/ episodes treated with penicillin and an aminoglycoside	Modification of penicillin/ aminoglycoside regimen	Response rate without modification	Response rate with modification	Total case fatality within first 30 days	Case fatality related to the initial febrile episode
Frøland, 1989	Randomized controlled trial	Acute leukemia	72 episodes	25%	69%	94%	6%	0%
Hammerstrøm, 1998	Retrospective chart review	Patients with leukemia and bacteremia	34 episodes	53%	47%	92%	8%	0%
Tangen, 1999	Retrospective chart review	Acute myelogenous leukemia	198 episodes	69%	25%	94%	8%	
Sigurdardottir, 2005	Prospective observational study	Cancers, mainly hematological malignancies	166 episodes				7%	0.8%
Torfoss, 2007	Randomized controlled trial	Cancers, mainly hematological malignancies	174 patients	60%	40%	99–100%	0.6%	0%
Stabel, 2008	Retrospective chart review	Pediatric cancers, 52% acute lymphoblastic leukemia	137 episodes	34%	66%	99–100%	$<1\%$	0%
Hammerstrøm, 2008	Retrospective chart review	Patients with leukemia or multiple myeloma and bacteremia					19%	
Total Norwegian studies		Cancers, mainly hematological malignancies	781 episodes	53%	47%	90–100%	5–10%	0–1%

The Frøland study was done with netilicin. Ten of 18 modifcations were a change from penicillin G to cloxacillin.
The Sigurdardottir and the Hammerstrøm 2008 studies focused on microbiological findings and did not report result of antibiotic therapy.
Empty boxes reflect numbers not presented in the publications.

Table II. Microbiological sensitivity in the Norwegian febrile neutropenia studies with penicillin G plus an aminoglycoside.

Study, Year of publication, (Years of data collection)	Type of study	Underlying malignancy	Gram-positive (GP) isolates	GP sensitive to penicillin G	GP sensitive to gentamicin	Gram-negative (GN) isolates	GN sensitive to amino-glycosides
Frøland, 1989 (1984–1988)	Randomized controlled trial	Acute leukemia	5			16	
Hammerstrøm, 1998 (1990–1995)	Retrospective chart review	Patients with leukemia and bacteremia	37	12/23	10/16 (netilmicin)	45	31/31 (tobramycin)
Tangen, 1999 (1990–1994)	Retrospective chart review	Acute myelogenous leukemia	41			45	45/45
Sigurdardottir, 2005[1] (1998–2000)	Prospective observational	Cancers, mainly hematological malignancies	48	29/46 63%	40/46 87%	57	57/57 100%
Torfoss, 2007 (2001–2005)	Randomized controlled trial	Cancers, mainly hematological malignancies	24	11/24	10/23 (tobramycin)	11	10/11 (tobramycin)
Stabel, 2008 (2002–2003)	Retrospective chart review	Pediatric cancers, 52% acute lymphoblastic leukemia	28			11	11/11
Hammerstrøm, 2008 (1995–2005)	Retrospective chart review	Patients with leukemia or multiple myeloma and bacteremia	179	75/152	38/62	180	98/100
Total Norwegian studies		Cancers, mainly hematological malignancies	314	98/199[2] 49%	58/101 57%	308	197/198 99%

[1]Hammerstrom, 2008, contributed with isolates to the study of Sigurdardottir, 2005. Information about how many isolates Hammerstrom contributed to the study of Sigurdardottir is not available. To avoid counting the same bacterial isolate twice, all Sigurdardottir's isolates are omitted from the Total Norwegians studies. [2]Streptococci were sensitive to penicillin G in 99% of the isolates. Gram-positive isolates resistant to both antibiotics were mainly coagulase-negative staphylococci and occational *Enterococcus faecium*. Empty boxes reflect numbers not presented in the publications.

metronidazol and fluconazol were allowed (Table I). The patients who needed a modification of the antibiotic treatment all had a successful outcome when followed for 30 days, except for one patient who died three weeks after being discharged from the hospital. This low fatality rate reflects the fact that patients already in septic shock were excluded according to routine recommendations. Septic shock is unusual in FN patients [10]. The mean time to modification of therapy of the initial antibiotic regimen was five days [9]. Modification within the first three days of the clinical course occurred in only 10% of the patients. The most common modifications were change to monotherapy with either ceftazidime or meropenem. Bacteremia was found in 31 patients (18%), six of whom were treated without modification [9]. Of the Gram-negative isolates, 91% were sensitive to tobramycin, and 46% of the Gram-positive isolates were sensitive to penicillin G. One patient with an *E. coli* resistant to tobramycin (MIC = 256 mg/l) did well with addition of ceftazidime on the second day of FN. The seven Gram-positive isolates that were resistant to both penicillin G and to tobramycin comprised four coagulase-negative staphylococci, two *Enterococcus faecium* and one Corynebacterium species. Altogether, eight isolates (26%) were resistant to both penicillin G and to tobramycin, a fact not preventing a benign outcome for all these patients. The mean increase of serum creatinine was 7 μmol/l and equally distributed between the two arms [9].

One retrospective pediatric study was published in 2007 [11]. Two hundred and thirty-six episodes of FN in 95 children were examined. Forty-nine of the patients had acute lymphoblastic leukemia. Blood cultures yielded growth in 39 episodes (17%). Penicillin G or ampicillin combined with an aminoglycoside was the initial empiric regimen in 58% of the episodes, and a regimen based on a third-generation cephalosporin, with a possibility to add other antibiotics, for example ampicillin to cover for Listeria species, was given to 42% of the patients (Table I). Unfortunately, the study does not report how many of the patients in the penicillin plus aminoglycoside arm who received penicillin G, and how many who received ampicillin. There were no statistically significant differences in outcome between the two regimens in terms of need to change the initial antibiotic regimen, days of fever, or maximum serum C-reactive protein values. Modification of the antibiotic regimen occurred in 34% of the episodes treated with penicillin G or ampicillin and an aminoglycoside, and in 31% of the episodes treated with a third-generation cephalosporin-based regimen. All 19 blood culture isolates were sensitive to at least one of the antibiotics in the penicillin and aminoglycoside

arm, whereas 16 of the 20 isolates were sensitive to at least one agent in the cephalosporin arm (Table II). One Gram-negative rod and three coagulase-negative staphylococcal isolates were resistant to all initial empiric antibiotics in the cephalosporin arm. One infection-related death (fungal septicemia) occurred during the period of the study.

Finally, Hammerstrøm et al. [7] published a follow-up study. A total of 322 episodes in 225 patients were analyzed. Most of the patients had acute leukemia or multiple myeloma. The most common isolates were *E. coli* (20%), coagulase-negative staphylococci (13%), and viridans streptococci (10%). There may have been an increase in enterococcal septicemias, especially ampicillin-resistant *E. faecium* septicemia (totally six isolates), since the first report of Hammerstrøm and Jacobsen 10 years earlier [5]. All 31 pseudomonas isolates were sensitive to tobramycin. Of the Gram-negative isolates, 98% were sensitive to aminoglycosides, and 49% of the Gram-positive isolates were sensitive to penicillin G (Table II). All-cause fatality rate within 30 days of bacteremia was 10% in the group of patients with acute leukemia. Infection was considered a contributing cause to a fatal outcome in 53% of those who died. All who died had an active malignancy, and most suffered a terminal condition. Twelve percent of the episodes were polymicrobial; among which enterococci were common, and the case fatality rate was higher. Hammerstrøm concluded that penicillin G and an aminoglycoside should still be the initial empiric regimen.

Some of the bacterial isolates from Hammerstrøm et al.'s 2008 study [7] also contributed to the study of Sigurdardottir [8]. This makes a total estimate of the number of isolates and their sensitivities towards penicillin G and towards gentamicin difficult. However, omitting the isolates from the study of Sigurdardottir from the total number of isolates, the total sentivities in the six remaining studies are the best possible estimates available (Table II). Unfortunately, it is not possible to calculate the exact number of isolates resistant to both penicillin G and to the aminoglycoside.

The NORM database is not specified according to neutropenia. The only information that exists concerning resistance and sensitivities in FN patients are the numbers based on these Norwegian trials (Table II). Moreover, NORM has never presented sensitivity information on viridans streptococci because of logistic problems related to representative clinical isolates and adequate microbiological identification. However, the NORM data document relatively stable Gram-negative sensitivity towards gentamicin, and almost no MRSA, VRE, or pneumococci resistant to penicillin.

How efficient is the combination of penicillin G plus an aminoglycoside and how marked is the nephrotoxicity of aminoglycosides in FN?

International antibiotic recommendations have documented that monotherapy with a broad-spectrum β-lactam antibiotic is excellent therapy in FN [12,13]. Moreover, the meta-analysis of Paul et al. [14] found that the addition of an aminoglycoside did not add to the efficacy of the antibiotic regimens and only caused more nephrotoxicity.

Klastersky summarized the EORTC-studies in FN in 1993 [15]. At that time, the combination of an antipseudomonal penicillin (usually carbencillin) and an aminoglycoside was the initial empiric antibiotic regimen of choice in FN. Klastersky concluded that evidence had shown that monotherapy with an aminoglycoside was suboptimal in FN.

However, there are reasons to assume that the combination of penicillin G and an aminoglycoside confers important synergistic effects compared to aminoglycoside monotherapy, discussed by Klastersky [15]. An in vitro trial [16] showed synergistic effects between β-lactams and aminoglycosides in resistant Gram-negative rods. *Pseudomonas aeruginosa* strains resistant to carbencillin showed a 10-fold increase in sensitivity to carbencillin when a small dose of gentamicin was added. Another study [17] indicated that synergy may occur between β-lactams, fluoroquinolones and aminoglycosides in *P. aeruginosa,* even though the strains were resistant to the individual antibiotics. Unfortunately, no studies have examined the effect of penicillin G and an aminoglycoside against Gram-negative rods, but there is reason to believe that this antibiotic combination, beside the additive effects by the differences in antibacterial resistance between the drugs, is more efficient than monotherapy with an aminoglycoside in FN.

Also, in the 1980's and earlier, there were few other antibiotic options if the initial antibiotic regimen failed. It is worth noting that many of the antibiotic trials performed with aminoglycosides in the 1970's used suboptimal doses of aminoglycosides [18–20]. In the said three studies gentamicin was given four times daily in doses of 0.75 mg/kg. The peak gentamicin levels aimed at was 4 mg/l, which in most cases is significantly lower than the 10–12 times the bacterial minimum inhibitory concentration (MIC) recommeded according to later insight in antibacterial pharmacodynamics [21]. In one study, gentamicin was administered as a continuous infusion [22], and gentamicin peak levels were kept at

4–5 mg/l. The patients received gentamicin for a minimum of seven days, or four days after becoming afebrile. Nephrotoxicity was described as azotemia, and major azotemia was defined as an increase in serum creatinine to above 2.5 mg/dl (191 μmol/l) or as an increase in serum BUN (urea) to above 50 mg/dl (18 mmol/l). Major azotemia occurred in 19% of the patients who had levels of gentamicin above 5 mg/l, but was unusual ("minor azotemia") at lower level ranges of gentamicin. Minor azotemia "was usually transient and of no clinical significance" [22]. These results may indicate that minor increases in creatinine secondary to aminoglycoside therapy are not clinically significant. In Norway, aminoglycosides are generally stopped when serum creatinine reaches 120 μmol/l.

Today, we have several different antibiotics at hand when the initial regimen proves unsatisfactory. The reason for using initial empiric penicillin G and an aminoglycoside in Norway is to avoid the use of more broad-spectrum β-lactam antibiotics than necessary. No other studies have, so far, compared penicillin G and an aminoglycoside with a broad-spectrum β-lactam.

Our clinical experience, based on the seven Norwegian studies, is that the penicillin G plus an aminoglycoside combination causes 50–60% of the patients to have their antibiotic regimen modified (Table I) whereas international therapy with a broad-spectrum β-lactam antibiotic leads to modifications in 30–40% of the patients. The frequency of case fatalities is similar in the Norwegian and in the international studies.

The Norwegian trial comparing tobramycin once against three times daily [9] found a mean maximum serum creatinine of 69 μmol/l (95% CI: 66–71 μmol/l). The highest absolute measured serum creatinine increase in this study was 47 μmol/l. Still, we are aware of the problem with nephrotoxicity. Patients who need further cis-platinum therapy are never treated with aminoglycosides to avoid compromising later vital anti-cancer chemotherapy.

Penicillin G and an aminoglycoside may promote less antibiotic resistance than therapy with broad-spectrum β-lactam antibiotics

Why do we insist on using the old-time, off-fashion antibiotic combination of penicillin G and an aminoglycoside? There are reasons to believe that penicillin G and an aminoglycoside is selecting for less resistance than broad-spectrum antibiotics [23]. The intestinal flora is the main location where resistance may develop. Theoretically, penicillin G does not affect the Gram-negative flora of the gut, and *E. coli* remains the predominant non-anaerobic Gram-negative rod in the fecal flora during therapy with penicillin G. Likewise, aminoglycosides are not excreted in the gut, and are not promoting β-lactamase-producing strains [23]. It would be unwise to abandon the practice of using a combination of penicillin G and an aminoglycoside as long as it works efficiently and remains acceptably safe for the patients, even if the hard evidence is lacking for the ecological benefits of this combination. We would rather encourage more research on this topic and on other antibiotic regimens, in order to better be able to evaluate the ecological impact of different antibiotic regimens.

There exist trials [24] comparing the effect of aminoglycoside and β-lactam combination therapy versus β-lactam monotherapy on the emergence of antimicrobial resistance. No benefit on the development of resistant strains was found when an aminoglycoside was added to the β-lactam regimen in this meta-analysis [24]. However, most of the studies in this meta-analysis evaluated broad-spectrum β-lactam antibiotics, and none of the studies compared penicllin G and an aminoglycoside with a broad-spectrum β-lactam regarding emergence of antimicrobial resistence.

However, there is ample evidence of the development of antibiotic resistance related to the amount of antibiotics consumed. The ESAC (European Surveillance of Antimicrobial Consumption) retrospective data collection (1997–2002) documented antibiotic hospital use in European countries [25]. In line with the NORM data [2], Norway belonged to the countries with the lowest antibiotic consumption. This study also documented a strong, positive correlation between the extent of antibiotic use in ambulatory and hospital care. The hospital practice seems to function as a model for the ambulatory care practitioners.

Already in 1983, McGowan [26] showed that increased prevalence of resistant organisms in hospitals was related to the use of antimicrobial agents. Unfortunately, there is too little evidence as to which antibiotics cause the most resistance problems in different situations, the relationship to other preventive measures, and how fast resistance may develop. In particular, we do not know the impact of intravenous aminoglycosides on the development of resistance, compared to oral antibiotics.

Furthermore, Austin et al. [27] points out that we should not wait for resistance to develop before we act, especially when we have a prescription tradition of penicillin G and an aminoglycoside, which seems to work well.

It is interesting to note that a leading international journal has taken a closer look at the Scandinavian tradition of using narrow-spectrum β-lactam antibiotics in combination with aminoglycosides, even though

this is not based on experience in FN patients. Freundlich's Danish historical cohort study from 2007 [28] was commented by the editor [29] concluding that "a large series of bacteremic patients from Denmark, treated either with a narrow-spectrum β-lactam or with a combination of a β-lactam and an aminoglycoside, shows comparable outcomes in the two groups." He further concludes, "In countries where the resistance is low enough to use 'old' β-lactams, and there is an unwillingness to use broad-spectrum β-lactams, evidence for the efficacy of combination treatment and for its role in keeping the resistance at a low level is wanting." Our conclusion fully supports this point of view; penicillin and an aminoglycoside is safe and effective initial empiric therapy in febrile neutropenia.

Conclusion

Norwegian bacterial resistance patterns, and the antimicrobial usage profiles, suggest that the policy of using penicillin G and an aminoglycoside in FN should continue. As long as the Gram-negative rods remain sensitive to the aminoglycosides and the streptococci remain sensitive to penicillin G, this combination seems to be an effective and safe initial empiric choice in FN. However, all such recommendation should always be reconsidered if the clinical response to penicillin G plus the aminoglycoside is not satisfactory. Thus, continuous surveillance and more investigations are necessary to monitor the Norwegian antibiotic consumption and microbiological epidemiological situations.

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