Antibiotic susceptibilties:
Gram negative bacteria

	% of strains susceptible		
Antibitoic	Klebsiella pneumoniae	Enterobacter cloacae	Pseudomonas aeruginosa
Gentamicin			
OSU hospital	87	92	60
NICU	100	100	100
Third generation cephalosporins			
OSU hospital	87	85	89
NICU	100	100	100

抗生物質感受性:
グラム陰性菌

	感受性 %		
抗生物質	Klebsiella pneumoniae	Enterobacter cloacae	Pseudomonas aeruginosa
ゲンタマイシン			
OSU hospital	87	92	60
NICU	100	100	100
第三世代セファロスポリン			
OSU hospital	87	85	89
NICU	100	100	100

Gram-negative bacilli isolated from the NICU, unlike those from the rest of the hospital and the community, changed little over the 12-year study period. Gram-negative bacilli showed reduced susceptibility in the rest of the hospital as compared to the NICU. For Klebsiella pneumoniae, gentamicin susceptibility was 87% hospital-wide versus 100% for the NICU. For the extended spectrum cephalosporins; Klebsiella pneumoniae susceptibility was 87% for the hospital and 100 % for the NICU. Eighty-nine percent of Pseudomonas aeruginosa strains were susceptible to ceftazidime hospital-wide and 100% for the NICU.

NICUで分離されたグラム陰性桿菌は、他の病院や一般社会とは異なり12年間ほとんど変わらなかった。グラム陰性桿菌に対する感受性はNICUに比較して他のユニットでは低下していた。Klebsiella pneumoniaeに対するゲンタマイシンの有効性は、NICUでは100%であったが病院全体では87%であった。広域セファロスポリンに対するKlebsiella pneumoniaeの感受性は、病院全体で87%、NICUでは100%であった。病院全体でのPseudomonas aeruginosaの89%はセフタジジムに感受性であり、NICUでは100%であった。

Antibiotic susceptibilities:
fungal isolates

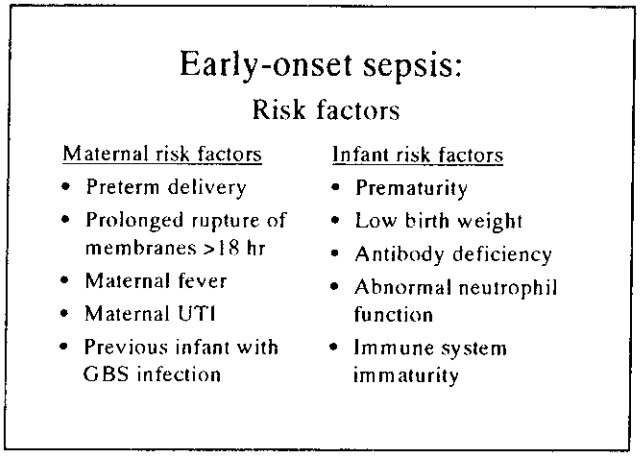
- All fungal isolates remained susceptible to Amphotericin B
- Fluconazole use increased during last study period
  - 2 resistant strains of C. albicans
  - 2 resistant strains of T. glabrata

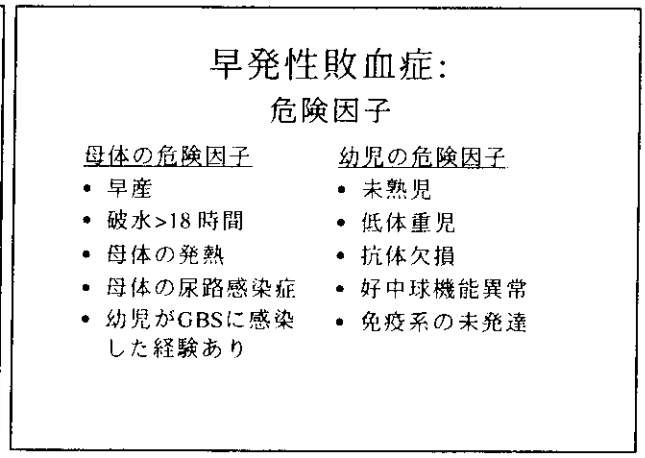
抗生物質感受性:
真菌

- 全ての真菌はアムホテリシンBに対し感受性を維持
- フルコナゾールの使用頻度はlast study の期間中に増加した
  - C. albicansの２つの耐性菌株
  - T. glabrataの２つの耐性菌株

Fungal isolates (all yeast) increased in prevalence in the last study period. Candida albicans, Candida parapsilosis, Malassezia furfur, and Torulopsis glabrata remained susceptible to amphotericin B throughout the 12-year study period. Fluconazole was used extensively in the hospital during the last study period and was accompanied by an increased prevalence of resistant Torulopsis glabrata and resistant strains of Candida. Two NICU strains of Candida albicans and both strains of Torulopsis glabrata were resistant to fluconazole. Amphotericn B remains the the agent of choice for treatment of fungal sepsis in premature infants.

真菌の分離株（すべて酵母菌）はlast study期間の流行により増加した。Candida albicans、Candida parapsilosis、Malassezia furfurおよびTorulopsis glabrataは、12年間を通してアムホテリシンB感受性であった。フルコナゾールはlast study期間に病院で広く使われた結果、耐性Torulopsis glabrataおよび耐性Candida菌による罹患率が増加した。Candida albicansの2つのNICU株、およびTorulopsis glabrataの2つの菌株はフルコナゾールに対し耐性であった。アムホテリシンBは、未熟児における真菌性敗血症の治療に引き続き用いられている薬剤である。





There are numerous factors that increase the neonate's risk of developing sepsis.[8] First of all, there are maternal risk factors that must be considered. Maternal illness such as urinary tract infection with bacteriuria or pyelonephritis with bacteremia increases the risk of neonatal sepsis. Prolonged rupture of membranes for greater than 18 hours has been shown to increase the risk of sepsis. This is due to the loss of a natural barrier against infection, as well as the loss of amniotic fluid which has antibacterial properties. The risk associated with prolonged rupture of membranes may be increased tenfold. The most significant maternal risk factor is chorioamnionitis.

Next to be considered are host risk factors of which prematurity is one of the most important.[8] This is due to immaturity of the immune system including defective granulocyte function, decreased complement concentrations, and abnormal opsonic activity. Maternal IgG antibodies do not cross the placenta until approximately 32 weeks gestation. Therefore, infants born before this lack protective antibodies.

新生児が敗血症に罹患する要因は多数存在する[8]。第一に、母体の危険因子について考えなければならない。細菌尿をともなう尿路感染症や菌血症をともなう腎盂腎炎に罹患した母体は、新生児敗血症の危険率を増大させる。18時間以上破水すると敗血症の危険率が増加する。これは抗菌的性質をもつ羊水がなくなったことと同時に、感染に対する本来持っていた防御機能がなくなったことが原因である。破水が長時間続くと、危険率は10倍にも増大した。母体の最も重要な危険因子は、絨毛羊膜炎である。

次に胎児の危険因子について考えなければならない。胎児の最も重要な危険因子の一つに早産が挙げられる[8]。これは、顆粒球機能の欠損、補体濃度の減少、オプソニン活性の異常を含む免疫系の未発達が原因である。母体のIgG抗体は妊娠約32週間まで胎盤を通過しない。従ってこれより前に生まれた幼児は防御機能をもつ抗体を欠くことになる。

Early-onset sepsis

Success of maternal intrapartum GBS antibiotic prophylaxis

- 1992 AAP guidelines for intrapartum GBS prophylaxis with ampicillin
- 54% decrease in GBS infections from first to last study period
- Decrease in mortality

早発性敗血症

GBS感染症予防のために分娩時母体に抗生物質投与を行うことによる成功

- アンピシリンによる分娩時GBS感染症予防のための1992年 AAP ガイドライン
- Firstからlast studyの間、GBS 感染症が５４%減少
- 死亡率の減少

Early-onset sepsis may be acquired in utero or during delivery, but its incidence can be influenced by antepartum antibitoic administration.[9] Most maternal antibiotic prophylactic programs have focused on eradications of Group B Streptococcal infections and the American Academy of Pediatrics (AAP) formalized its recommendations for antepartum GBS antibiotic prophylaxis in 1992.[10] Later, in 1996 the Centers for Disease Control in Atlanta, Georgia in conjunction with the AAP and the American College of Obstetrics and Gynecology (ACOG) revised the guidelines.[11] The success of these guidelines in reducing early-onset sepsis due to GBS has been published[12] and is also evident in our NICU by the 56% reduction in early-onset sepsis and the corresponding reduction in neonatal deaths due to group B Streptococcal infections from the first to the last study period.

We have not observed an increase in the prevalence or severity of bloodstream infections due to S. aureus that, at least in our NICU, remained methacillin-susceptible throughout the study period.

早発性敗血症は子宮内、もしくは分娩時に発現するかもしれない。しかしその発現率は分娩前の抗生物質の投与によって回避され得る[9]。母体への抗生物質投与による多くの予防プログラムは、Group B Streptococcus感染の根絶に焦点を合わせている。American Academy of Pediatrics (AAP) は分娩前のGroup B Streptococcusの予防を目的とした抗生物質の投与を1992年に正式に推薦した[10]。後の1996年に、ジョージア州アトランタのCenters for Disease Control はAAPやAmerican College of Obstetrics and Gynecology (ACOG) と合同してガイドラインを改正した[11]。Group B Streptococcusによる早発性敗血症を減少させたこれらガイドラインの成功について公表された[12]。さらに、我々のNICUにおいてfirst studyからlast studyにかけて早発性敗血症が56%減少し、Group B Streptococcus感染による新生児の死亡も同様に減少したことが明らかとなった。

少なくとも我々のNICUでは研究期間中、メチシリンに感受性を持つS. aureusによる血流感染症の罹患率の増加、または危険性を我々は経験しなかった。

Early-onset sepsis
Gram negative bacteria

- E. coli responsible for approximately half the cases of gram negative infections in both study periods
- Associated with prematurity & high mortality (25%)
- Increased ampicillin resistance
- Remained sensitive to gentamicin

早発性敗血症
グラム陰性菌

- グラム陰性菌感染症の約半分はE. coliが原因
- 早産及び高死亡率(25%)と関連
- アンピシリン耐性菌の増加
- ゲンタマイシン感受性の維持

The prevalence of early-onset sepsis due to gram-negative bacilli during the entire study period remained low. As expected, E. coli was responsible for one half of the cases and was associated with prematurity and high mortality. The number of ampicillin-resistant isolates from early-onset sepsis increased, but this trend was not associated with an increase in mortality. E. coli remained 100% susceptible to gentamicin.

Ampicillin and gentamicin have been the preferred antibiotics for treatment of early-onset neonatal sepsis for over 30 years. Because epidemics due to organisms resistant to aminoglycosides have been described, surveillance and infection control are critical. White et.al. reported that the extensive use of ampicillin and gentamicin as first choices for suspected sepsis did not increase the prevalence of resistant organisms and that there was no association between sepsis-related death and ampicillin resistant gram negative bacteria.[13]

The decision not to use third generation cephalosporins as a first choice in the treatment of suspected sepsis was based on reports that routine use of cephalosporins leads to antimicrobial resistance among gram-negative bacteria more rapidly than the use of aminoglycosides.[14,15]

全研究期間の間、グラム陰性桿菌による早発性敗血症の罹患率は低値を維持した。予想通りE. coliによる症例が半数を占め、早産および高死亡率と関連していた。早発性敗血症由来のアンピシリン耐性菌の数は増加したが、この傾向は死亡率の増加とは関連していなかった。E. coliのゲンタマイシンに対する感受性は100%のまま維持された。

アンピシリンおよびゲンタマイシンは30年以上もの間、新生児の早発性敗血症の治療に選ばれた抗生物質であった。アミノグリコシド耐性菌による流行には、サーベイランスおよび感染管理が重要である。Whiteらは、敗血症が疑われたときの第一選択薬としてアンピシリンやゲンタマイシンを広範囲に使用することは耐性菌の出現を増加させないこと、また、敗血症に関連した死亡とアンピシリン耐性グラム陰性菌との間には関連がないことを報告した[13]。

第三世代セファロスポリンを敗血症が疑われたときの第一選択薬としては使用しないという決定は、その日常的な使用によってアミノグリコシドより更に急速にグラム陰性菌の抗生物質に対する耐性獲得に繋がるという報告に基づいている[14,15]。

Nosocomial infections: Risk factors

- Prematurity
- Umbilical vessel catheters
- Deep venous catheters
- Mechanical ventilation
- Parenteral nutrition
- Multiple courses of antibiotics
- Corticosteroid therapy
- Poor hand washing compliance

院内感染: 危険因子

- 未熟児
- 臍帯血管カテーテル
- 中心静脈確保
- 機械的ガス交換
- 非経口栄養
- 抗生物質の連用
- コルチコステロイド治療
- 手洗いの未実施

Prematurity, low birth weight and invasive procedures such as umbilical vessel catheterization, deep venous line placement, mechanical ventilation are all risk factors for late-onset sepsis. Certain drug therapies also increase the risk of nosocomial infectiions such as total parenteral nutrition, multiple courses of antibiotics, particularly broad spectrum antibiotics, and the use of corticosteroids for bronchopulmonary dysplasia. The environment also plays an important role in the development of nosocomial infections making clean equipment and scrupulous hand washing essential.

未熟児、低体重児、臍帯血管カテーテル法のような侵襲的処置、中心静脈確保、機械的ガス交換はすべて遅発性敗血症の危険因子となる。特定の薬物治療すなわち、高カロリー輸液（TPN)、抗生物質の連用（特に広域性スペクトルをもつ抗生物質の使用)、気管支肺形成異常のためのコルチコステロイドの使用によっても院内感染の危険性は増加する。環境面での配慮、すなわちクリーンな設備、徹底的な手洗いの施行は院内感染の発生に重要な役割を果たす。

Late-onset sepsis:
Gram negative bacteria

- Bloodstream infections due to gram negative bacteria increased by 328%
  - E. coli
  - Klebsiella pneumoniae
  - Enterobacter cloacae
- High morbidity and mortality
- Increased survival of VLBW infants & longer hospital stays increase risk of infection

遅発性敗血症:
グラム陰性菌

- グラム陰性菌による血流感染症は 328% 増加
  - E. coli
  - Klebsiella pneumoniae
  - Enterobacter cloacae
- 高い罹患率と死亡率
- 極低体重幼児の生存率増加及び長期入院による感染症の危険増加

Late-onset bloodstream infections due to gram-negative bacteria increased by more than threefold and resulted in high morbidity and mortality. Increases in the prevalence of E. coli, Klebsiella pneumoniae, and Enterobacter cloacae are of concern. Fortunately, the strains from our NICU remained sensitive to gentamicin, third generation cephalosporins, and extended-spectrum penicillins.

グラム陰性菌による遅発性血流感染症は3倍以上増加し、高い罹患率と死亡率を引き起こした。E. coli、Klebsiella pneumoniae および Enterobacter cloacaeによる罹患率の増加が関与している。幸いにも、我々のNICUの菌株はゲンタマイシン、第三世代セファロスポリンおよび広域ペニシリンに対して高い感受性を維持した。

Late-onset sepsis:

Vancomycin & gentamicin antibiotic protocol

- Coagulase-negative Staph accounted for 60% of total bloodstream infections in both study periods
  - Remained susceptible to vancomycin
- If blood culture results showed gram negative bacteria, vancomycin discontinued and ceftazidime initiated

遅発性敗血症:

バンコマイシン、ゲンタマイシン
抗生物質管理プロトコール

- Coagulase-negative Staph による血流感染症は両研究期間ともに 60% を占めた
  - バンコマイシン感受性の維持
- 血液培養の結果グラム陰性菌が検出されたら、バンコマイシンを中止し、セフタジジムを開始

The choice of vancomycin and gentamicin in combination to treat suspected late-onset sepsis was based on the likelihood that coagulase-negative Staphylococcus or gram negative bacteria were the most likely pathogens. All of the coagulase-negative Staph species remained susceptible to vancomycin throughout the 12-year study period. The stable antibiogram for isolates from our NICU made antibiotic adjustments in individual patients uncommon. However, if culture results revealed a gram negative organism, vancomycin was discontinued and ceftazidme was added to gentamicin.

遅発性敗血症の疑いに対する治療としてのバンコマイシンおよびゲンタマイシン併用を選んだのは、コアグラーゼ陰性Staphylococcus、またはグラム陰性菌がその原因として最も考え得る病原体であるという理由に基づいていた。12年の研究期間を通して、コアグラーゼ陰性Staphylococcus属の全てはバンコマイシンに対して感受性を維持していた。NICUにおて単離した菌に対する抗菌スペクトル一覧表を用いて、個々の患者への抗生物質の調整を行った。しかし、培養した結果グラム陰性菌であることが明らかとなった場合は、バンコマイシンは中止し、セフタジジムをゲンタマイシンに加え投与した。

Antibiotic policies

- Reviewed annually
- Based on antibiotic susceptibilities from our NICU, not the entire hospital

抗生物質使用指針

- 毎年再検討
- 病院全体からではなく、NICUからの抗生物質に対する感受性に基づく

Our antibiotic policies which are reviewed annually, are based only on antibiotic susceptibility information from our unit, not from the hospital at large or from national antibiotic resistance data. We agree with Stratton et.al. that focused microbiological surveillance by hospital units is more valuable, because hospital-wide data may suggest antibiotic resistance where there is none or mask severe resistance problems unique to some care units.[16]

我々の抗生物質の使用指針は毎年検討されているが、病院全体もしくは国の抗生物質に対する耐性菌データからではなく、我々のユニットからの抗生物質の感受性の情報にのみ基づいている。Strattonらが提唱する、病院のユニット単位での微生物のサーベイランスに焦点を当てることに我々は同意する。なぜなら、病院レベルでは耐性菌に関するデータは全くないか、もしくはいくつかのケアユニットだけの特有の重篤な耐性菌の問題を見逃すかもしれないからである[16]。

Hospital-wide antibiotic policy changes in 1997

- Increased prevalence methicillin-resistant Staph aureus (MRSA)
- Increased incidence of vancomycin-resistant enterococcus faecium (VRE)
  - Severe restriction on use of cephalosporins
  - Encourage use of extended spectrum penicillins and fluoroquinolones
  - Enforce appropriate use of po & IV vancomycin
  - Restrict use of vancomycin as prophylaxis

病院の抗生物質使用指針 1997年に改訂

- Methicillin-resistant Staph aureus (MRSA) による感染者増加
- Vancomycin-resistant enterococcus faecium (VRE)の発生増加
  - セファロスポリンの使用を厳重に制限
  - 広範囲スペクトルのペニシリン及びフルオロキノロン系薬剤の使用を奨励
  - 適切な経口、静注バンコマイシンの使用
  - 予防的なバンコマイシンの使用は制限

Because of the hospital-wide increase in incidence of methacillin-resistant staphylococcus aureus (MRSA) and vancomycin-resistant enterococcus faecium (VRE), hospital-wide antibiotic policies were changed in November 1997 to bring these organisms under control. Neither of these organisms was a problem in the NICU.

Review of antibiotic use hospital-wide revealed that cephalosporins were being extremely overused. Since the spectrum of the cephalosporins does not cover Enterococcus, this overuse was felt to be a cause of selection and overgrowth of these organisms. Then the overuse of vancomycin may contribute to the increasing resistance problem.

In an attempt to bring infections caused by these organisms under control, several changes in antibiotic policies were made. All of the cephalosporins were taken off the hospital formulary except cefazolin and cefepime. Cefotetan become a "resitricted use" antibitotic which could only be used for one dose surgical prophylaxis and pelvic inflammatory disease. A program using pharmacists to decrease the use of cephalosporins was initiated. Whenever a cephalosporin was ordered, the pharmacist investigated and suggested an extended spectrum penicillin or fluoroquinolone if appropriate.. Oral vancomycin could no longer be used for Clostridium difficile enterocolitis unless the patient had already failed metronidazole therapy. The use of vancomycin for surgical prophylaxis was severely restricted.

These hospital-wide antibiotic policy changes did not affect the NICU controlled antibiotic program to any great extent. Ampicilin and gentamicn are still used for early-onset sepsis and vancomycin and gentamicin remained the choice for empiric antibiotic therapy for suspected late-onset sepsis. The only difference is if the blood cultures grow a gram-negative bacteria, an extended spectrum penicillin such as piperacillin is added rather than ceftazidime after the vancomycin is discontinued.

Methicillin-resistant Staphylococcus aureus (MRSA) および Vancomycin-resistant enterococcus faecium (VRE) の院内での発生率の増加に伴い、これらの菌を管理する目的で院内における抗生物質の使用指針を1997年11月に変更した。これらの細菌のどちらも、NICUでは問題にならなかった。

院内での抗生物質の使用を評価することにより、セファロスポリン系薬剤が高頻度に使用されていることが明らかとなった。セファロスポリン系薬剤のスペクトルはEnterococcusをカバーしていないので、この高頻度な使用はこれら細菌を残し繁殖させる原因に繋がると思われた。高頻度なバンコマイシンの使用は、耐性菌増加の問題の一因となるかもしれない。

管理下においてもこれら細菌による感染が発生したことにより、抗生物質の使用指針のいくつかが変更された。セファゾリンおよびセフェピムを除く全てのセファロスポリン系薬剤は、病院の医薬品集から削除された。セフォテタンは"使用制限されるべき"抗生物質に該当し、外科的予防、骨盤の炎症性疾患のため1回のみ使用される。セファロスポリン系薬剤の使用を減らすために、薬剤師が実施するプログラムが開始された。セファロスポリンが処方されたときは必ず薬剤師は調査し、広域ペニシリン、またはフルオロキノリンが適用できる場合にはこれらを薦めた。メトロニダゾールで治療できなかったときを除いて、経口剤としてのバンコマイシンはクロストリジウム・ディフィシル小腸結腸炎には用いられないであろう。外科的予防のためのバンコマイシンの使用は厳しく制限された。

これらの院内における抗生物質の使用指針の変更は、NICUで管理された抗生物質のプログラムにほとんど影響をおよぼさなかった。アンピシリンおよびゲンタマイシンはいまだに早発性敗血症に用いられ、バンコマイシンとゲンタマイシンは遅発性敗血症の疑いに対して経験的な選択薬として残っている。唯一の違いは、血液培養によりグラム陰性菌が出現したとき、セフタジジムよりピペラシリンのような広域ペニシリンがバンコマイシンの中止後に加わることである。

Summary

- Decrease in early-onset sepsis due to group B Strep
- Increased survival & length of hospitalization for small premature infants parallels the increase in late-onset bloodstream infections
- Limited use of third generation cephalosporins prevented resistance

Summary

- Group B Strepによる早発性敗血症の減少
- 未熟児の生存期間及び入院期間の延長と遅発性の血流感染症の増加と相関
- 第三世代抗生物質セファロスポリンの使用制限による耐性菌の発現防止

In summary, there has been a decrease in the prevalence of early-onset sepsis due to group B Streptococcus, which is attributable to the efficacy of maternal antepartum antibiotic prophylaxis programs. Increased survival and length of hospitalization for the small premature infants are paralleled by an increase in late-onset bloodstream infections due to coagulase-negative Staphylococcus and gram-negative bacteria. The combination of ampicillin and gentamicin for suspected early-onset sepsis and vancomycin and gentamicin for suspected late-onset sepsis has not resulted in antimicrobial resistance in our NICU. Successful treatment of individual sepsis cases was facilitated by the preservation of antimicrobial susceptibilities. Our controlled antibiotic program limited the empirical use of cephalosporins in treatment of early- and late-onset sepsis and avoided resistance to this class of antibiotics. The absence of serious outbreaks or epidemics highlights the usefulness of controlled antibiotic programs and the need for periodic reevaluations of antimicrobial resistance based on individual care units and not on hospital-wide or national data.

まとめとして、Group B Streptococcusによる早発性敗血症は減少したが、このことは母体に対する分娩前の抗生物質投与による予防プログラムの効力に起因していた。小さな未熟児の生存期間や入院期間の延長は、コアグラーゼ陰性Staphylococcusやグラム陰性菌による遅発性の血流感染症の増加と相関している。早発性敗血症が疑われる患者へのアンピシリンとゲンタマイシンの併用、または遅発性敗血症が疑われる患者へのバンコマイシンとゲンタマイシンの併用をしても、我々NICUでは抗生物質耐性菌の発現に繋がらなかった。個々の敗血症の症例に対する適切な治療は、抗生物質に対する感受性を維持することにより容易になった。我々が管理した抗生物質プログラムは、早発、または遅発性の敗血症に対する治療におけるセファロスポリンの経験的使用を制限し、耐性菌の出現を回避した。危険な感染や流行を回避できたことは、抗生物質プログラムが有用であったことを意味し、病院や国家レベルではなく個々のケアユニットでの抗生物質耐性菌の定期的な再評価が必要であることを強調している。

Bloodstream infections in a Neonatal Intensive Care Unit:
12 Year's Experience with an Antibiotic Control Program

References

1. Moore DL. Nosocomial infections in newborn nurseries and neonatal intensive care units. In: Mayhall CG, ed. Hospital Epidemiology and Infection Control. Baltimore, MD: Maple Press; 1996:535-564.

2. Peter G, Cashore WJ. Infections acquired in the nursery: epidemiology and control. In: Remington JS, Klein JO, eds. Infectious Disease of the Fetus and Newborn Infant. 4th ed. Philadlphia, PA: W.B. Saunders Co; 1995:1264-1286.

3. Freeman J, Epstein MF, Smith NE, et.al. Extra hospital stay and antibiotic usage with nosocomial coagulase-negative staphylococcal bacteremia in two neonatal intensive care unit populations. Am J Dis Child. 1990;144:324-329.

4. Simon C, Schroder H, Beyer C, et.al. Neonatal sepsis in an intensive care unit and results of treatment. Infection. 1991;19:146-149.

5. Tessin I, Trollfors B, Thiringer K, et.al. Ampicillin-aminoglycoside combinations as initial treatment for neonatal septisemia or meningitis. Acta Paediatr. 1991;80:911-916.

6. Modi N, Damjanovic V, Cooke RWI, Outbreak of cephalosporin resistant Enterobacter cloacae infection in a neonatal intensive care unit. Arch Dis Child. 1987;62:148-151.

7. Coovadia YM, Johnson AP, Bhana RH, et.al. Multiresistant Klebsiella pneumoniae in a neonatal nursery: the importance of Maintenance of infection control policies and procedures in the prevention of outbreaks. J Hosp Infect. 1992;22:197-205.

8. Kaftan H and Kinney JS. Early-onset neonatal bacterial infections. Seminars in Perinatology. 1998;22:15-24.

9. Boyer KM. Selective intrapartum prophylaxis of neonatal group b streptococcal early-onset disease : Interruption of mother to infant transmission. J Infect Dis. 1983;148:810-816.

10. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidelines for prevention of group B streptococcal infection by chemoprophylaxis. Pediatrics. 1992;90:775-778.

11. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal infection. Pediatrics. 1997;99:489-496.

12. Schrag SJ, Zywicki S, Farley MM, et.al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. N Engl J Med. 2000;342:15-20.

13. White RD, Townsend TR, Stephens MA, et.al. Are surveillance of resistant enteric bacilli and antimicrobial usage among neonates in a newborn intensive care unit useful? Pediatrics. 1981;68:1-4.

14. Bryan CS, John JF, Pai MS, et.al. Gentamicin vs. cefotaxime for therapy of neonatal sepsis. Am J Dis Child. 1985;139:1086-1089.

15. Chow JW, Fine MJ, Shlaes DM, et.al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med. 1991;115:585-590.

16. Stratton CW, Ratner H, Johnston PE, et.al. Focused microbiologic surveillance by specific hospital unit as a sensitive means of defining antimicrobial resistance problems. Diagn Microbiol Infect Dis. 1992;15:11S-18S.

"Providing Patient – Specific Drug Information"

(個々の患者に応じた医薬品情報の提供)

by Karim A. Calis, Pharm.D.,

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Curriculum Vitae

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EDUCATION

University of Maryland
College Park, Maryland
Pre-Pharmacy Studies
1979-1981

University of Maryland School of Pharmacy
Baltimore, Maryland
Bachelor of Science in Pharmacy
May 1984

University of Maryland School of Pharmacy
Baltimore, Maryland
Doctor of Pharmacy
May 1986

School of Hygiene and Public Health
The Johns Hopkins University
Master of Public Health
May 1995

PROFESSIONAL EXPERIENCE

Pharmacy Extern, Peoples Drug Stores, Rockville, Maryland, 1980 - 1983

Pharmacist, Gray Drug Fair, Potomac, Maryland, Summer 1984

Staff Pharmacist, Department of Pharmacy Services, Holy Cross Hospital
Silver Spring Maryland, September 1984 - March 1986

Clinical Coordinator, Department of Pharmacy, Suburban Hospital, Bethesda, Maryland,
June 1986 - August 1988

Assistant Director, Clinical Services, Department of Pharmacy, Suburban Hospital
Bethesda, Maryland, August 1988 - December 1989

Director, Nutrition Support Team, Suburban Hospital, Bethesda, Maryland
October 1987 - December 1989

Coordinator, Drug Information Service, Clinical Center Pharmacy Department
National Institutes of Health, Bethesda, Maryland, December 1989 - Present

Clinical Specialist, Endocrinology & Women's Health, Developmental Endocrinology Branch, Pediatric and Reproductive Endocrinology Branch
National Institute of Child Health and Human Development
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health, Bethesda, Maryland, December 1989 - Present

Preceptor, Drug Information and Pharmacotherapy, Pharmacy Practice Residency, NIH, 1989- Present

Program Director, ASHP-Accredited Specialized Residency in Drug Information Practice and Pharmacotherapy, NIH, 1992-Present

Clinical Assistant Professor, Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy, June 1987 - July 1996

Assistant Professor, Department of Pharmacy Practice, Howard University College of Pharmacy and Pharmacal Sciences, November 1992 - Present

Clinical Associate Professor, Department of Pharmacy Practice and Science
University of Maryland School of Pharmacy, July 1996 - Present

Associate Clinical Professor, Department of Pharmacy and Pharmaceutics
Medical College of Virginia, Virginia Commonwealth University, August 1996 - Present

CURRENT PROFESSIONAL ACTIVITIES

- Member, Pharmacy and Therapeutics Committee, NIH
- Chairman, Cytokines Subcommittee, NIH
- Chairman, Antimicrobials Subcommittee, NIH
- Member, Institutional Review Board, National Institute of Child Health and Human Development
- Coordinator, Pharmacy Journal Club, NIH
- Animal Model Committee, NIH
- Editor, *Pharmacy Update,* NIH
- IV Task Force, NIH
- Research Committee, Holy Cross Hospital, Silver Spring, Maryland
- Clinical Pharmacy Preceptor, University of Maryland School of Pharmacy
- Council of Pharmacists, Drug Topics
- Editorial Board (medical informatics), Cybermedix, Inc., Springfield, Virginia

- Clinical Reviewer and Consultant, Health Information Designs, Inc., Arlington, Virginia
- Reviewer of ASHP Midyear Clinical Meeting and Annual Meeting Contributed Papers
- Referee
  - Hospital Formulary
  - American Journal of Health-System Pharmacy
  - Pharmacotherapy
  - Annals of Pharmacotherapy
  - Biopharmaceutics and Drug Disposition
  - Hospital Pharmacy
  - The New England Journal of Medicine
  - Journal of the American Medical Association
  - Journal of the American Pharmaceutical Association
- Editor
  - "Pharmacotherapy Pipeline" Column
  - *Pharmacotherapy*
- Contributor
  - *United States Pharmacopeia Dispensing Information (USP DI)*
  - United States Pharmacopeia
- Reviewer
  - *American Hospital Formulary Service*
  - American Society of Health-System Pharmacists
- Assistant Editor, DRUGDEX System, Micromedex, Inc.
- Site Coordinator and Participant, Drug Surveillance Network, Center for Pharmacoepidemiology Research, State University of New York, Buffalo, New York
- Member, Mid Atlantic Pharmacy Cholesterol Council, National Pharmacy Cholesterol Council
- Expert Panel on Nutrition and Electrolytes, United States Pharmacopeia

ASHP
- Program Director, ASHP-accredited Specialized Residency in Drug Information Practice
- Referee for the *American Journal of Health-System Pharmacy*
- Contributor to *AJHP* and *Clinical Pharmacy* (See citations)
- Presenter at Midyear/Annual Meetings (See citations)
- Educational Programming Associate
- Reviewer for Midyear and Annual Meeting Contributed Papers
- Member, Nutrition and Drug Information SPGs and various SPG committees
- Member, Editorial Board, *American Journal of Health-System Pharmacy*

RESEARCH

Principal Investigator
- Pilot study of cimetidine-aided creatinine clearance to assess glomerular filtration rate in children.
- A comparison of chloral hydrate and orally administered midazolam for sedation of pediatric patients undergoing diagnostic imaging procedures.

- Evaluation of the quality of pharmacotherapy consultations provided by U.S. drug information centers.

Associate Investigator

- Transdermal androgen replacement therapy for young women with spontaneous premature ovarian failure.
- Investigation of the human immune response in normal subjects and patients with disorders of the immune system and cancer.
- The use of metformin to improve fertility in clomiphene-resistant hyperandrogenic anovulation: A double-blinded, placebo-controlled study.
- Autoimmune premature ovarian failure: a controlled trial of alternate-day prednisone therapy.
- Effect of diltiazem on renal function in cyclosporine-treated uveitic patients.
- Low-dose continuous infusions of urokinase with or without heparin to treat fibrinous occlusion of tunneled venous access devices: a randomized, double-blind study.
- Cyclodextrin itraconazole in the treatment of mucocutaneous candidiasis in HIV-infected children.
- The efficacy of pharmacological intervention in preventing hypertensive cerebrovasculopathy.
- Linkage analysis in families, linkage by identity by descent in sib-pairs, and candidate gene analysis in the stuttering population.
- Use of flutamide in clomiphene-resistant anovulation.
- Efficacy of troglitazone in the treatment of patients with severe insulin resistance and lipodystrophy.
- Evaluation of the clinical utility of a computerized, patient-driven medication history in the detection and management of adverse drug effects.
- Low-dose continuous infusions of urokinase with or without heparin to treat fibrinous occlusion of tunneled venous access devices: a randomized, double-blind study.
- Hydroxychloroquine pharmacokinetics in a patient with systemic lupus erythematosus undergoing continuous ambulatory peritoneal dialysis.
- Ovulation induction in patients with karyotypically normal spontaneous premature ovarian failure.

RECENT PUBLICATIONS

- Grothe DR, Calis KA, Jacobsen L, et al. Olanzapine pharmacokinetics in pediatric and adolescent inpatients with childhood-onset schizophrenia. J Clin Psychopharmacol. (In press)
- Heck AM, Yanovski JA, Calis KA. Orlistat, a new lipase inhibitor for the management of obesity. Pharmacotherapy 2000;20(3):270-9.
- Semba CP, Murphy TP, Bakal CW, Calis KA, Matalon TA. Thrombolytic therapy with use of alteplase (rt-PA) in peripheral arterial occlusive disease: review of the clinical literature. J Vasc Interv Radiol 2000;11(2):149-61.
- Calis KA, Cullinane AM, Horne MK. Bioactivity of cryopreserved alteplase solutions. Am J Health-Syst Pharm 1999; 56:2056-7.

- Masucci IP, Calis KA, Bartlett DL, et al. Thrombocytopenia after isolated limb or hepatic perfusions with melphalan: the risk of heparin-induced thrombocytopenia. Ann Surg Oncol 1999; 6(5):476-80.
- Bloch M, Stager S, Braun A, Calis KA, Turcasso NM, Grothe DR, Rubinow DR. Pimozide-induced depression in men who stutter. J Clin Psychiatry 1997;58(10):433-6.
- Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy 1997;17(4):729-36.
- Meyer CC, Calis KA. New hemodialysis membranes and vancomycin clearance. Am J Health-Syst Pharm 1995;52:2794-6.

CURRENT PROFESSIONAL AFFILIATIONS

- American College of Clinical Pharmacy
- American Society for Parenteral and Enteral Nutrition
- American Society of Health-System Pharmacists
  - Drug Information SPG
    - Research Forum Review Committee
    - Strategic Planning Committee
  - Nutrition Support SPG
  - Member, Committee on Public Policy and Government Relations
- Chesapeake College of Clinical Pharmacy
- Drug Information Association
- International Society for Pharmacoepidemiology
- Kappa Psi Pharmaceutical Fraternity
- League of Intravenous Therapy Education
- Maryland Society for Parenteral and Enteral Nutrition
- Maryland Society of Hospital Pharmacists
- Professional Section, American Diabetes Association
- Society for Epidemiologic Research
- University of Maryland Alumni Association
- Washington Metropolitan Society of Hospital Pharmacists

HONORS

- Founding Editor, 1983
  Pharmakon, University of Maryland School of Pharmacy
- Recognition of Excellence as Pharmakon Editor, May 1984
  Newsletter, University of Maryland School of Pharmacy
- Clinical Clerkships Completed With Honors, 1984 - 1986
  Ambulatory Care Medicine, Inpatient Medicine (3 clerkships), Clinical Research
- Outstanding Young Men of America, 1988
- Hospital Pharmacist of the Year - 1989
  Washington Metropolitan Society of Hospital Pharmacists
- Squibb Leadership Award, 1993
- Mckesson Leadership Award, 1993

Providing Patient-Specific Drug Information

Karim Anton Calis, Pharm.D., M.P.H., BCPS, BCNSP, FASHP

OBJECTIVES

- Develop strategies to overcome the impediments that prevent pharmacists from providing effective responses and recommendations
- Outline the procedures that are necessary to identify the true drug information needs of the requester
- List the four critical factors that should be considered and systematically evaluated when formulating a response
- Define analysis and synthesis and explain how they are employed in the process of formulating responses and recommendations
- List the elements and characteristics of effective responses to drug information queries

INTRODUCTION TO THE NIH

Begun as a one-room Laboratory of Hygiene in 1887, the National Institutes of Health today is one of the world's foremost medical research institutions. The NIH mission is to uncover new knowledge that will lead to better health for everyone. NIH works toward that mission by conducting research in its own laboratories; supporting the research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helping in the training of research investigators; and fostering communication of medical information. The NIH is one of eight health agencies of the Public Health Service which, in turn, is part of the U.S. Department of Health and Human Services. Comprised of the Warren G. Magnuson Clinical Center, the National Library of Medicine, and 25 separate Institutes and Centers, the NIH has 75 buildings on more than 300 acres in Bethesda, MD. The NIH budget in 1999 was $15.6 billion. Approximately 82 percent of the budget is spent on grants and contracts supporting research and training in more than 2,000 research institutions throughout the U.S. and abroad. These grants and contracts comprise the NIH Extramural Research Program. Approximately 10 percent of the budget goes to NIH's Intramural Research Programs, the more than 2,000 projects conducted mainly in its own laboratories.

個々の患者に応じた医薬品情報の提供

Karim Anton Calis, Pharm.D., M.P.H., BCPS, BCNSP, FASHP

【目的】

- 薬剤師が効果的に回答や提言を行う際に，障害となっているものを取り除くための方策を述べる
- 依頼者が本当に必要としている医薬品情報を見つけ出すための手順を概説する
- 回答を系統立てて作成する際，考察し，系統的に評価すべき４つの重要項目をリストアップする
- 分析と統合を明確にし，回答と提言を作成する上でどのように利用するかを説明する
- 医薬品情報関連の質問に対する有効な回答の要素と特徴をリストアップする

NIHの紹介

1887年に一室の衛生研究所として始まったNIHは，今日，世界の最先端の医学研究機関の１つです。NIHの使命は，全ての人がより健康になれるような新しい知見を生み出すことです。NIHは独自の研究施設での研究実施，海外を含めた総合大学，医科大学，病院および研究機関における外国籍の科学者の研究支援，研究者のトレーニングの支援，医学情報コミュニケーションの促進により，その使命を果たしています。NIHは，公衆衛生局の８つの健康機関のうちの１つで，アメリカ保健福祉省の一部でもあります。NIHは，Warren G. Magnuson Clinical Center，国立医学図書館および25の研究所やセンターで構成され，メリーランド州ベセスダの300エーカー以上の土地に75の建物を所有しています。1999年のNIHの予算は156億ドルで，そのうち約82%の使途は米国や海外の2,000以上の研究機関における研究やトレーニングの支援を目的とした助成および契約です。これらの助成および契約にはNIHの外部の研究プログラムも含まれます。予算の約10%はNIHの内部の研究プログラム，すなわち，主にNIHの研究所で実施される2,000以上のプロジェクトに当てられます。