Chloramphenicol: A Review of Its Use in Clinical Practice

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Chloramphenicol has certain notable characteristics: it penetrates reliably into the central nervous system; it is usually bacteriostatic, but is bactericidal for Hemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis; it is metabolized in the liver, and levels of drug in serum need to be monitored in patients with liver disease and in neonates. Potential toxicity limits the use of this drug. It has been estimated that death from aplastic anemia occurs in one of 24,500-40,800 courses of treatment. The incidence of aplastic anemia after parenteral therapy is unknown; however, only a few cases have been reported. The gray baby syndrome occurred in premature and newborn infants receiving high or unmodified doses of chloramphenicol. This condition can be avoided by reduction of dosage and by monitoring levels of drug in the serum of these infants. The most common toxicity is a reversible, dose-related bone marrow suppression, which is identified by serial monitoring of reticulocyte and complete blood cell counts. Many of the indications for use of this drug are still controversial because studies comparing the toxicity and efficacy of chloramphenicol and of alternative antibiotics have not been done.

Introduced in 1949, chloramphenicol, the first broad-spectrum antibiotic, quickly gained acceptance. It could be given orally or parenterally; it was easily synthesized and inexpensive; and it was thought to have no significant toxicity. In 1950, Rich et al. [1] reported aplastic anemia, and Volini et al. [2] described a dose-related bone marrow suppression; both conditions were associated with the use of chloramphenicol. In 1959, Sutherland [3] reported the gray baby syndrome in premature and newborn infants who had received high-dose chloramphenicol therapy. As a result of the toxicity of this drug and the development of safer alternative antibiotics, the indications for use of chloramphenicol narrowed and its use declined. Recently, with the appearance of ampicillin-resistant Hemophilus influenzae and the increased knowledge of the pathogenicity of Bacteroides fragilis in pelvic and intraabdominal infections, chloramphenicol has reemerged as an important antibiotic. Our purpose is to present a review of the pharmacology, spectrum of activity, toxicity, and clinical usages of this drug.

Pharmacology

As the parent compound, chloramphenicol is available in capsules for oral administration. Unmodified chloramphenicol cannot be given easily as a suspension because it is extremely bitter; it cannot be given parenterally because it is insoluble. These problems can be circumvented by use of the two esters of chloramphenicol. Chloramphenicol palmitate is tasteless in suspension and can be taken by patients who cannot swallow capsules. Chloramphenicol succinate is a water-soluble ester suitable for iv use. These esters have no antimicrobial activity [4-6], but, after oral or iv administration, they are hydrolyzed at variable but usually rapid rates [4-6] and circulate as unesterified chloramphenicol. Chloramphenicol succinate is hydrolyzed by the liver, lungs, and kidneys. In infants, 1 hr after iv administration, 17% of the drug in the serum remains as chloramphenicol succinate whereas 83% is unesterified [7]. Chloramphenicol palmitate is hydrolyzed to chloramphenicol prior to gastrointestinal absorption. A

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The half-life of chloramphenicol is 1.6–3.3 hr in adults [21], whereas in infants and children the range is 0.87–17.8 hr, with a mean of 5.94 hr [22]. In anuric adults the half-life increases only slightly to between 3.2 and 4.2 hr [21], and the nontoxic metabolite, chloramphenicol glucuronide, accumulates. In patients with liver disease or immature liver function (premature infants and neonates), the rate of metabolism of chloramphenicol may be decreased [23, 24]. In patients with advanced cirrhosis, the half-life of this drug may increase to between 3 and 12 hr [21]. This longer half-life may correlate with the increased level of bilirubin and the decreased level of albumin in serum [23, 24]. In patients with immature liver function or liver disease, levels of chloramphenicol in serum cannot be predicted reliably, and these levels must be monitored to avoid dose-related toxicity. Toxicity can usually be avoided by maintenance of serum concentrations of <25 μg of chloramphenicol/ml [25]. Both chloramphenicol and bilirubin are metabolized in the liver; however, they do not compete and, therefore, this drug does not increase levels of bilirubin in serum [26].

Chloramphenicol has been shown to inhibit the metabolism of tolbutamide, diphenylhydantoin, and dicumarol [27, 28]. As a result, it may be necessary to decrease the dosage of these drugs when they are used simultaneously with chloramphenicol. In animals, phenobarbital can increase the rate of metabolism of chloramphenicol [29]. Black et al. [30] speculated that this interaction was the cause for decreased levels of chloramphenicol in the serum of a neonate treated simultaneously with both of these drugs. However, Koup et al. [28] reported that chloramphenicol decreased the rate of metabolism of phenobarbital. When these two drugs were used together, this decrease resulted in unexpectedly high levels of phenobarbital in serum. Unfortunately, the interaction between these two drugs has not been adequately defined, and, at the present time, it is advisable to monitor levels of both chloramphenicol and phenobarbital in serum when these drugs are used simultaneously.

Chloramphenicol penetrates well into most tissues [31] and tissue fluids such as synovial fluid [32], pleural fluid [5], ascites fluid [33], aqueous humor [34], sputum [35], breast milk [36], and the cerebrospinal fluid in both inflamed and uninfamed meninges [5, 37–39]. Levels of chloramphenicol in the cerebrospinal fluid of adults are ~50% of levels achieved in serum [5, 39]. In newborns and young infants, penetration is better; levels of drug in cerebrospinal fluid are 50%–99% of levels in serum [7, 22].

The recommended dose of chloramphenicol for adults and children older than four weeks of age is 50–100 mg/kg per day. This dose will usually give levels of drug in serum in the therapeutic range [9, 40] of 10–20 μg/ml. For premature infants and infants less than two weeks old, the recommended
dose is 25 mg/kg per day; for infants two to four weeks old, the recommended dose is 50 mg/kg per day. However, the levels of chloramphenicol in serum are unpredictable in infants less than four weeks of age [30, 41]; therefore, to avoid toxic accumulation (levels of >25 \( \mu \text{g/ml} \)) [25] of this drug and to assure levels in the therapeutic range, serum levels must be monitored.

Spectrum of Activity

Table 1 shows the spectrum of activity of chloramphenicol. This drug is also active against organisms not listed in the table, such as streptococci, Neisseria species, corynebacteria, Listeria, and anaerobes. It is frequently active against Salmonella and Shigella and is also active against less frequently recovered pathogens, such as Rickettsia [42-44], Chlamydia [44], Mycoplasma [45], Treponema pallidum [46, 47], Borrelia [44], Leptospira [47], Pseudomonas pseudomallei [48], and Actinomycetes [44]. It is not active against Pseudomonas aeruginosa, mycobacteria, fungi, and parasites.

Chloramphenicol is generally bacteriostatic, blocking bacterial protein synthesis by reversible inhibition of the peptidyl transferase reaction at the 50S subunit of the bacterial ribosomes [49]. However, this drug is usually bactericidal for H. influenzae [50-52], Streptococcus pneumoniae [50, 52], and Neisseria meningitidis [50, 52]. Overvort et al. [51] tested 297 isolates of H. influenzae type b and found, with chloramphenicol, a median MIC of 0.4 \( \mu \text{g/ml} \) and a median MBC of 0.8 \( \mu \text{g/ml} \).

In 1951, Jawetz et al. [53] demonstrated in vitro antagonism between chloramphenicol and penicillin by showing that chloramphenicol could inhibit the early rapid killing effect of penicillin. In this study [53] and in others [54-56], chloramphenicol had to be administered before the penicillin in order to demonstrate antagonism. Antagonism caused by chloramphenicol can be explained by the recent observation [57] that this drug can inhibit bacterial autolytic enzymes that contribute to rapid bacterial killing in the presence of penicillin. In contrast to the studies demonstrating in vitro antagonism between these two drugs [53-55], other studies showed synergism [58-60] or an additive effect [55]. The clinical relevance of possible antagonism, synergism, or additive effect is still open to question. Two clinical studies [61, 62]

### Table 1. Sensitivities to chloramphenicol of bacterial isolates obtained from patients at Hartford Hospital (Hartford, Conn.), 1980.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total no. of isolates tested</th>
<th>Percentage susceptible to chloramphenicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilus influenzae type b</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Hemophilus influenzae, nontypeable</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Citrobacter</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Proteus morganii (Morganella morganii)</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Proteus rettgeri*</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>Providencia*</td>
<td>25</td>
<td>72</td>
</tr>
<tr>
<td>Serratia</td>
<td>50</td>
<td>88</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>Bacteroides fragilis group</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Bacteroides melaninogenicus</td>
<td>19</td>
<td>100</td>
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<tr>
<td>Bacteroides species</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>Fusobacterium</td>
<td>14</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE: Sensitivities were determined by the microdilution method; MIC for aerobes was \( \leq 8 \mu \text{g/ml} \) (exception: MIC for Hemophilus influenzae was \( \leq 4 \mu \text{g/ml} \); for anaerobes, the Wilkins-Chalgren broth microdilution method was used.

* Isolates of Proteus rettgeri and Providencia were gathered in 1979 and tested by disk diffusion method.
have reported possible antagonism between a penicillin and chloramphenicol for treatment of meningitis. In a prospective study of meningitis, Mathies et al. [61] reported the deaths of six (4.1%) of 145 patients treated with ampicillin alone and 14 (11.4%) of 123 patients treated with ampicillin, chloramphenicol, and streptomycin (the latter used for only the first two days of therapy). However, these studies were not repeated and the results have not been duplicated. Lindberg et al. [62] reported that children with meningitis due to H. influenzae had more eighth-nerve sequelae when treated with ampicillin and chloramphenicol than when treated with ampicillin alone, whereas the mortality of both groups was equal. However, this study was neither randomized nor controlled, and the number of infants studied was too small to make meaningful conclusions.

Toxicity

The use of chloramphenicol is limited by its toxicity. Two types of toxicity induced by this drug are potentially fatal: aplastic anemia, which is idiosyncratic, and the gray baby syndrome, which is dose-related. A third type of toxicity is a dose-related bone marrow suppression.

In 1950, Rich et al. [1] reported the first case of aplastic anemia associated with chloramphenicol: this condition occurred in a 63-year-old man with pyuria who had received this drug intermittently for three months. Since this report, there have been ~700 cases [63-68] of chloramphenicol-related blood dyscrasias in the United States. Most of these were cases of aplastic anemia. Unfortunately, chloramphenicol-associated aplastic anemia cannot be predicted by the monitoring of blood cell counts and, when it occurs, it frequently does so weeks or months after use of the drug. The mortality for patients who develop aplastic anemia associated with chloramphenicol is ~50%; however, the prognosis is poorest if aplastic anemia develops two months or more after administration of the drug [69].

In 1952, reports of aplastic anemia associated with chloramphenicol prompted the U.S. Food and Drug Administration (FDA) to conduct a national survey of blood dyscrasias [63]. Of 296 cases of aplastic anemia reported, 139 involved patients who had received chloramphenicol before developing this condition, and 68% of this latter group had had intermittent or prolonged therapy with chloramphenicol. After this survey, labels were required warning that blood dyscrasias may be associated with intermittent or prolonged use of chloramphenicol and that the drug should not be used for minor infections or indiscriminately. In a 1954 survey of 349 cases of aplastic anemia, only 80 cases were associated with chloramphenicol, and in most of these the patient had received the drug prior to the 1952 warning [64]. Therefore, from 1952–1954, there was a reduction in the number of cases of aplastic anemia associated with chloramphenicol; this reduction was perhaps due to a reduction in usage of the drug.

In 1953, the American Medical Association established the Registry on Blood Dyscrasias, which accumulated data on drugs associated with aplastic anemia. Best [66] reviewed 408 cases of blood dyscrasias associated with chloramphenicol that occurred from 1953–1964. He found that this drug had been prescribed for inappropriate or trivial infections such as the common cold, bronchitis, tonsillitis, and acne. In 39% of the cases, patients had received chloramphenicol intermittently. Not surprisingly, since this drug was more frequently prescribed for women than for men, 62% of those cases reviewed by Best affected women. Finally, Best [66] reported a mortality of ~50%, and nonwhite patients had a better prognosis than did whites. In 1970, the Registry on Blood Dyscrasias was discontinued but not without argument in favor of continuing it [70].

Most surveys of blood dyscrasias associated with chloramphenicol lacked information on the use of this drug. However, in 1969 Wallerstein et al. [67] studied the relationship between the use of chloramphenicol and fatal aplastic anemia in California from 1963–1964. They estimated that fatal aplastic anemia associated with this drug occurred in one of 24,500–40,800 courses of treatment and found that fatal aplastic anemia was 13 times more common in patients treated with chloramphenicol than in those who had no exposure to chloramphenicol during that year. They also noted that the incidence of idiopathic aplastic anemia (unassociated with chloramphenicol) increased with age (figure 1). Unfortunately, no information about chloramphenicol usage by age groups was available, and, therefore, no correction for age was made. Consequently, no definite conclusions can be made regarding the apparent
chloramphenicol is hard to prove because of other variables, such as old age and exposure to other drugs, which are associated with aplastic anemia.

The association of aplastic anemia with the use of oral preparations of chloramphenicol [71, 72] has led some clinicians to administer this drug exclusively by the iv route, which now appears to be the preferred route for inpatients. Thus, in a university study of 100 inpatients who received chloramphenicol [77], only four patients received an oral preparation. Also, in a study of 202 inpatients at a community hospital who received this drug, only four patients received oral chloramphenicol [78]. The association of aplastic anemia with the oral preparation may be due in part to the fact that a larger number of patients received oral preparations of this drug. Unfortunately, data are not available comparing the incidence of aplastic anemia after administration of oral vs. parenteral chloramphenicol and, therefore, firm conclusions cannot be drawn concerning their relative safety.

A recent editorial [79] discussing the advantages of oral chloramphenicol for the treatment of meningitis caused by H. influenzae stated that in countries where oral chloramphenicol is available without a prescription the incidence of aplastic anemia is not increased and implied that the association between the oral preparation and aplastic anemia is lacking. It is important to emphasize that the association of oral chloramphenicol with aplastic anemia is firm, and that what is not known is whether parenteral exposure alone also increases the incidence of aplastic anemia. In countries where oral chloramphenicol may be used indiscriminately, the lack of cases of aplastic anemia most likely reflects a failure of detection or of reporting. Until better data are available, the best estimate of risk of fatal aplastic anemia following the use of chloramphenicol is one for every 24,500-40,800 courses of treatment [67], while the risk may be less with parenteral therapy. This estimate of risk of fatal aplastic anemia associated with the use of chloramphenicol can be put into better perspective when it is realized that parenteral penicillin G is associated with fatal anaphylaxis in one of 50,000-67,000 (11 of 800,000 to four of 200,000) treated patients [80]. In a smaller study involving 94,655 patients treated with penicillin, one death from anaphylaxis was recorded [81].

![Figure 1. Frequency of death from idiopathic aplastic anemia (unassociated with chloramphenicol) by age.](image)

Clustering of chloramphenicol-associated aplastic anemia in the elderly. Also, in contrast to prior observations by Best [66], Wallerstein et al. [67] found that all their cases of aplastic anemia associated with chloramphenicol occurred in black patients.

Most cases of aplastic anemia associated with chloramphenicol have occurred after oral administration of the drug [71, 72]. In fact, to our knowledge, there are only six cases in the literature where chloramphenicol-associated aplastic anemia occurred after parenteral exposure [67, 68, 73-76]. Since 1971, 41 cases of aplastic anemia associated with this drug have been reported to the FDA (personal communication; M. Dreis, U.S. Food and Drug Administration, Drug Experience Division, Rockville, Md.). Three of these cases were associated with parenteral administration only. In one of these three cases, a complete record was sent to the FDA. This case involved a 66-year-old man who was treated prophylactically with iv chloramphenicol succinate for coronary artery bypass surgery. Approximately 10 days after the drug had been stopped, the patient developed aplastic anemia. Two weeks later the patient died from sepsis, and an autopsy confirmed the diagnosis of aplastic anemia. In this patient, as in all previously reported isolated cases, the definite association between aplastic anemia and parenterally adminis-
In addition to reports of aplastic anemia associated with orally and parenterally administered chloramphenicol, cases of aplastic anemia after prolonged use of chloramphenicol ophthalmic preparations have been reported [82–84]. The first reported case involved a patient [82] who developed aplastic anemia after using 10 ml of a 0.5% chloramphenicol suspension each month for 23 months. Another patient [84] developed aplastic anemia after using 6.5 ml of a 0.5% chloramphenicol suspension over the course of a year. Finally, a fatal case of aplastic anemia was reported in a 33-year-old man who used chloramphenicol–polymyxin B ophthalmic ointment intermittently for four months [84]. With only these case reports as evidence, the causal association of aplastic anemia with chloramphenicol ophthalmic preparations is not definite.

Theories regarding the pathogenesis of chloramphenicol-associated aplastic anemia have proliferated. A 1960 communication to the Registry on Blood Dyscrasias [66] reported aplastic anemia in a twin exposed to chloramphenicol while the other twin developed thrombocytopenia after administration of this drug. Then, in 1969, Nagao and Mauer [85] reported aplastic anemia in identical twins common environmental exposures could not be ruled out, these findings led to speculation about a genetic predisposition. It was theorized [86] that a genetic metabolic defect induced by chloramphenicol resulted in damage to undifferentiated marrow stem cells [87].

A second hypothesis suggests that certain enteric bacteria can produce a specific enzyme that degrades chloramphenicol to a toxic product [71]. The rarity of these enzyme-producing enteric bacteria could explain the infrequency of aplastic anemia. It is a tempting explanation of the apparent association of aplastic anemia with the oral forms of this drug.

A third theory was advanced by Yunis [88], who speculated that the p-nitrosulfathiazole group is responsible for aplastic anemia by inhibiting DNA synthesis in marrow stem cells. His theory was based on the observation that thiampenicol, a chloramphenicol derivative not possessing a p-nitrosulfathiazole group (figure 2) and used in Europe, has not been associated with aplastic anemia.

A fourth theory [89] proposes that for chloramphenicol to cause aplastic anemia, there must be some preexisting marrow damage. This theory is based on studies of mice in which pretreatment with busulfan to induce marrow damage resulted in marrow stem cell loss upon subsequent challenge with chloramphenicol.

The monitoring of blood cell counts cannot be relied upon to predict aplastic anemia, since the irreversible stage of this disease occurs before changes are seen. However, periodic monitoring is valuable for detection of dose-related marrow suppression. The first signs of chloramphenicol-induced marrow suppression are increased levels of iron in serum and vacuolation of marrow erythroid precursors [25], a process which is associated with electron microscopic changes in mitochondrial ultrastructure of bone marrow cells [90]. Reticulocytopenia, which can be seen three to five days after initiation of treatment with chloramphenicol, occurs either at the same time as [9] or after the increase in concentration of iron in serum [25]. A fall in hemoglobin and platelet counts [25, 91] can occur after reticulocytopenia. Neutropenia, a rare manifestation of suppression by chloramphenicol, can occur after the fall in concentration of hemoglobin [25, 91]. Unfortunately, this sequence of suppression is not always apparent, and suppression of one blood element alone can occur. Bone marrow suppression occurred in 18 of 21 adults treated with 6 g of chloramphenicol per day, a dose that was associated with trough levels of drug in serum of >25 μg/ml [25]. Suppression occurred in two of 20 adult patients receiving 2 g of chloramphenicol per day, a dose that was associated with trough levels of drug in serum of <10 μg/ml [22].

Vacuolation of marrow erythroid and myeloid precursors is not specific for marrow suppression induced by chloramphenicol since it also occurs in alcoholism, DiGuglielmo syndrome, riboflavin deficiency, and phenylketonuria [92]. By the ad-
ministration of phenylalanine, Ingall et al. [93] reversed the marrow vacuolation associated with chloramphenicol therapy. They proposed that chloramphenicol inhibited the incorporation of phenylalanine into proteins (since chloramphenicol is similar in structure to uridine phosphate) and that a uridine triplet is the genetic code for phenylalanine. In a subsequent study [94], however, the protective effect of phenylalanine was not duplicated.

In a recent controlled study [95], a regimen of chloramphenicol plus gentamicin was compared to a regimen of clindamycin plus gentamicin or ticarcillin plus gentamicin for treatment of abdominal or pelvic sepsis. The rates of development of anemia (2%–4.5%) and leukopenia (0–1.5%) were similar among the three treatment groups; however, the group receiving chloramphenicol plus gentamicin had higher rates of reticulocytopenia (14% vs. 2% in the other groups) and thrombocytopenia (9.5% vs. 2% in the other groups). It is interesting to note that in this study [95] the rates of occurrence of anemia were similar among the three groups.

For patients receiving chloramphenicol, it is recommended that a hemoglobin determination and reticulocyte, platelet, and white blood cell counts be done initially and then every three to four days. If marrow suppression develops, it may be reversed by discontinuation of the drug or by reduction of the dose until trough levels measure <25 µg/ml.

The gray baby syndrome was described by Weiss et al. [96] in 1960 as "abdominal distention, with or without emesis; progressive pallid cyanosis, vasomotor collapse, frequently accompanied by irregular respiration; and sometimes death within a few hours of onset of these symptoms." It occurred [97] in premature and full-term infants who received >100 mg of chloramphenicol/kg per day for three to five days. It is theorized that chloramphenicol at high levels inhibits electron transport within mitochondria [98] and that this inhibition causes circulatory collapse. The gray baby syndrome is avoided by use of the recommended reduced dosage of chloramphenicol for premature infants and neonates. Inadvertent overdosage of this drug can also cause an adult form of the gray baby syndrome, as was seen in a man who was mistakenly given 20 g of chloramphenicol by rapid infusion (with a resulting level of drug in serum of 201 µg/ml) and who went into shock characterized by circulatory collapse, cyanosis, and coma [99]. Overdosage of chloramphenicol has been successfully treated with exchange transfusion [100] or charcoal-column hemoperfusion [101].

With the exception of gross overdosage, the gray baby syndrome has been well documented only in infants younger than 30 days of age and in premature infants. A six-week-old infant with bacterial meningitis was reported to have developed the gray baby syndrome 12 hr after therapy with im chloramphenicol succinate had been initiated [102]; however, in this case, shock seems likely to have been due to inadequate treatment of the meningitis with im chloramphenicol. Craft et al. [103] noted the occurrence of the gray toddler syndrome in three infants six to 25 months old who had received chloramphenicol. However, these infants also had received iv sulfadimidine.

Allergic reactions associated with the administration of chloramphenicol are rare. This drug has not caused anaphylaxis, and only once has it been convincingly reported to have caused drug fever [104]. Two infrequent adverse effects associated with this drug include optic neuritis [105–107] (related to chronic use) and hemolytic anemia in patients with the glucose-6-phosphate dehydrogenase deficiency of the Mediterranean variant who were treated with chloramphenicol for typhoid fever [108, 109]. Additional adverse effects include such gastrointestinal reactions as nausea, unpleasant metallic aftertaste, stomatitis, and diarrhea [110]. Dermatologic reactions include vesicular and maculopapular eruptions [110], but these reactions are rare.

Chloramphenicol has been shown to be an immune suppressant [111, 112]. When compared with controls, adults treated with this drug have shown a decreased anamnestic response to tetanus toxoid; however, the clinical significance of this effect is not known [111]. Also, chloramphenicol has been shown to suppress cell-mediated immunity in vitro [112].

Clinical Indications
Chloramphenicol is the drug of choice for few infections. It is indicated for initial treatment of serious infections caused by ampicillin-resistant H. influenzae [113]. For patients allergic to peni-
cillin, chloramphenicol is the drug of choice for meningitis caused by *H. influenzae*, *S. pneumoniae*, or *N. meningitidis* [114].

A combination of chloramphenicol and ampicillin has been recommended as initial therapy [115] for pediatric patients with meningitis possibly due to *H. influenzae*; then, if the organism is determined to be ampicillin-sensitive, chloramphenicol can be discontinued. Although chloramphenicol alone is effective initial therapy for meningitis [116] caused by *H. influenzae*, *S. pneumoniae*, or *N. meningitidis*, the addition of ampicillin is recommended for infants and children because of the rare occurrence of resistance of *H. influenzae* to chloramphenicol [117-119]. However, the futility of such an approach (attempting to cover for all possibilities of drug resistance) was brought into clearer focus recently when meningitis due to *H. influenzae* type b that was resistant to both chloramphenicol and ampicillin was reported [120]. A recent report [121] of 1,885 cases of meningitis due to *H. influenzae* stated that 18% of the isolates were resistant to ampicillin and none were resistant to chloramphenicol. Because resistance of *H. influenzae* to chloramphenicol is very rare [117-119] and, if present, can be determined rapidly [122], we recommend an alternate approach to management of bacterial meningitis in infants and children. In order to avoid potential antagonism between chloramphenicol and ampicillin, we would advise initial therapy with chloramphenicol alone and then a continuation of this drug or a change to ampicillin (if the organism is sensitive). Studies comparing different therapeutic approaches are necessary to define optimal management of meningitis due to *H. influenzae*.

Chloramphenicol is considered by some clinicians to be the drug of choice for typhoid [123, 124] and enteric [72, 122] fevers if these conditions are caused by bacterial strains susceptible to chloramphenicol [125]. Recent studies comparing oral therapies have shown that either trimethoprim-sulfamethoxazole [126-128] or amoxicillin [129] is as effective as chloramphenicol for typhoid fever. However, no large studies have yet been done comparing iv chloramphenicol with other antibiotics by this route.

Because of its ability to penetrate the blood-brain barrier and its activity against the organisms usually causing brain abscess (especially *B. fragilis*), chloramphenicol is one of the drugs of choice for the treatment of brain abscess [124, 130-133] before the identification of the causative organism or organisms. It is indicated for meningitis and other infections of the central nervous system caused by gram-negative bacilli that are resistant either to ampicillin or to other antibiotics that penetrate well into the central nervous system. Resistance to chloramphenicol, however, can develop during therapy [134, 135]. Aminoglycosides are an alternative to chloramphenicol but, when given parenterally, they penetrate poorly into the cerebrospinal fluid [136]. Unfortunately, when given intrathecally [137] or intraventricularly [138], aminoglycosides did not increase the rate of survival of neonates with meningitis due to gram-negative bacilli over the rate of survival for those treated by the parenteral route only.

The use of chloramphenicol becomes controversial when alternative antibiotics could be administered. It is frequently difficult to decide which antibiotic is less toxic and clinically more effective. Both in vitro and clinical studies have shown that either chloramphenicol or clindamycin is effective for anaerobic infections [139-141]. Because pelvic and abdominal sepsis are frequently caused in part by anaerobes, including *B. fragilis*, chloramphenicol or clindamycin is indicated in the initial therapy. Carbenicillin, cefoxitin, and metronidazole are also effective against the anaerobes, including most *B. fragilis*; however, there are no large controlled clinical studies comparing these antibiotics to chloramphenicol. In a more recent controlled study [95] involving 175 patients with serious abdominal or pelvic sepsis due to mixed aerobic and anaerobic organisms, chloramphenicol, clindamycin, and ticarcillin given concomitantly with gentamicin were equally effective. Anaerobic pulmonary infections, even when *B. fragilis* is present, usually respond to penicillin alone [132], and thus the routine use of chloramphenicol is unnecessary for these infections.

Either chloramphenicol or tetracycline is effective for rickettsial infections [142-145]. In young children or pregnant women, for whom tetracycline is contraindicated, chloramphenicol should be used. Although a few cases of successful therapy with chloramphenicol have been reported [146, 147], this drug is not indicated for treatment of bacterial endocarditis because it is usually bacteriostatic. Clinical results of its use for such infections have been poor [146, 148, 149].
Chloramphenicol has few indications for patients outside the hospital setting. Unfortunately, it has been used for the treatment of trivial infections in some patients and, in a number of these, aplastic anemia has developed [67, 69]. The misuse of chloramphenicol was emphasized in a 1973–1974 Tennessee study of outpatients [150] which showed that, out of 1,061 prescriptions for chloramphenicol, only one was deemed indicated.

In conclusion, chloramphenicol is a valuable antibiotic with proven effectiveness and firm indications. The potential for development of fatal aplastic anemia (one of 24,500–40,800 treatment courses) must be considered whenever this drug is used [67]; however, this toxicity is best put into perspective when it is realized that parenteral penicillin is associated with fatal anaphylaxis in about one of every 67,000 treated patients [80]. The association of aplastic anemia with oral forms of chloramphenicol has been well established, whereas the association of this disease with parenteral administration needs further study. Reinstating a registry for chloramphenicol-associated blood dyscrasias is one step in this direction. Finally, controversy concerning the toxicity of and indications for chloramphenicol will continue until controlled prospective studies comparing this drug with alternate antibiotics are completed.

References


