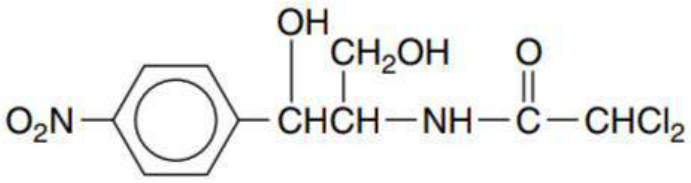
Chloramphenicol, an antibiotic produced by *Streptomyces venezuelae*, was introduced into clinical practice in 1948. With the drug's wide use, it became evident that chloramphenicol could cause serious and fatal blood dyscrasias. For this reason, chloramphenicol is now reserved for treatment of life-threatening infections (e.g., meningitis, rickettsial infections) in patients who cannot take safer alternatives because of resistance or allergies (Wareham and Wilson, 2002).



CHLORAMPHENICOL

The antibiotic is unique among natural compounds in that it contains a nitrobenzene moiety and is a derivative of dichloroacetic acid. The biologically active form is levorotatory.

Antimicrobial Activity. Chloramphenicol possesses a broad spectrum of antimicrobial activity. Strains are considered sensitive if they are inhibited by concentrations of ≤8 μg/mL, except *S. pneumoniae where the breakpoint is* 4 μg/mL, and *H. influenzae*, which has a breakpoint of 2 μg/mL. Chloramphenicol is bacteriostatic against most species, although it may be bactericidal against *H. influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*. More than 95% of strains of the following gram-negative bacteria are inhibited *in vitro* by 8 μg/mL or less of chloramphenicol: *H. influenzae*, *N. meningitidis*, *N. gonorrhoeae*, *Brucella* spp., and *Bordetella pertussis*. Likewise,

most anaerobic bacteria, including gram-positive cocci and *Clostridium* spp., and gram-negative rods including *B. fragilis*, are inhibited by this concentration of the drug. Strains of *S. aureus* tend to be less susceptible, with MICs >8 µg/mL. Chloramphenicol is active against *Mycoplasma*, *Chlamydia*, and *Rickettsia*.

The Enterobacteriaceae are variably sensitive to chloramphenicol. Most strains of *Escherichia coli* (≥75%) and *Klebsiella pneumoniae* are susceptible. *Proteus mirabilis* and indole-positive *Proteus* spp. are susceptible. *P. aeruginosa* is resistant to even very high concentrations of chloramphenicol. Strains of *V. cholerae* have remained largely susceptible to chloramphenicol. Strains of *Shigella* and *Salmonella* resistant to multiple drugs, including chloramphenicol, are prevalent. Of special concern is the increasing prevalence of multiple-drug-resistant strains of *Salmonella* serotype typhi, particularly for strains acquired outside the U.S.

Mechanism of Action. Chloramphenicol inhibits protein synthesis in bacteria, and to a lesser extent, in eukaryotic cells. The drug readily penetrates bacterial cells, probably by facilitated diffusion. Chloramphenicol acts primarily by binding reversibly to the 50S ribosomal subunit (near the binding site for the macrolide antibiotics and clindamycin, which chloramphenicol inhibits competitively). Although binding of tRNA at the codon recognition site on the 30S ribosomal subunit is undisturbed, the drug apparently prevents the binding of the amino acid–containing end of the aminoacyl tRNA to the acceptor site on the 50S ribosomal subunit. The interaction between peptidyltransferase and its amino acid substrate cannot occur, and peptide bond formation is inhibited (Figure 55–2).

Chloramphenicol also can inhibit mitochondrial protein synthesis in mammalian cells, perhaps because mitochondrial ribosomes resemble bacterial ribosomes (both are 70S) more than they do the 80S cytoplasmic ribosomes of mammalian cells. The peptidyltransferase of mitochondrial ribosomes, but not of cytoplasmic ribosomes, is inhibited by chloramphenicol. Mammalian erythropoietic cells are particularly sensitive to the drug.

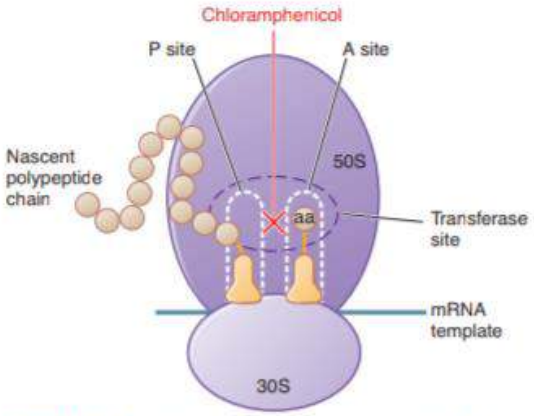


Figure 55–2. *Inhibition of bacterial protein synthesis by chloramphenicol.* Chloramphenicol binds to the 50S ribosomal subunit at the peptidyltransferase site and inhibits the transpeptidation reaction. Chloramphenicol binds to the 50S ribosomal subunit near the site of action of clindamycin and the macrolide antibiotics. These agents interfere with the binding of chloramphenicol and thus may interfere with each other's actions if given concurrently. See Figure 55–1 and its legend for additional information.

Resistance to Chloramphenicol. Resistance to chloramphenicol usually is caused by a plasmid-encoded acetyltransferase that inactivates the drug. Resistance also can result from decreased permeability and from ribosomal mutation. Acetylated derivatives of chloramphenicol fail to bind to bacterial ribosomes.

Absorption, Distribution, Fate, and Excretion. Chloramphenicol is absorbed rapidly from the GI tract, and peak concentrations of 10-13 µg/mL occur within 2-3 hours after the administration of a 1-g dose. The product for oral administration is no longer available in the U.S. The preparation of chloramphenicol for parenteral use is the water-soluble, inactive prodrug sodium succinate. Similar concentrations of chloramphenicol succinate in plasma are achieved after intravenous and intramuscular administration. Hydrolysis of chloramphenicol succinate by esterases occurs *in vivo*. Chloramphenicol succinate is rapidly cleared from plasma by the kidneys; this may reduce overall bioavailability of the drug because as much as 30% of the dose may be excreted before hydrolysis. Poor renal function in the neonate and other states of renal insufficiency result in increased plasma concentrations of chloramphenicol succinate. Decreased esterase activity has been observed in the plasma of neonates and infants, prolonging time to peak concentrations of active chloramphenicol (up to 4 hours) and extending the period over which renal clearance of chloramphenicol succinate can occur.

Chloramphenicol is widely distributed in body fluids and readily reaches therapeutic concentrations in CSF, where values are ~60% of those in plasma (range, 45-99%) in the presence or absence of meningitis. The drug actually may accumulate in the brain. Chloramphenicol is present in bile, milk, and placental fluid. It also is found in the aqueous humor after subconjunctival injection.

Hepatic metabolism to the inactive glucuronide is the major route of elimination. This metabolite and chloramphenicol itself are excreted in the urine following filtration and secretion. Patients with cirrhosis or otherwise impaired hepatic function have decreased metabolic clearance, and dosage should be adjusted in these individuals. The $t_{1/2}$ of chloramphenicol correlates with plasma bilirubin concentrations. About 50% of chloramphenicol is bound to plasma proteins; such binding is reduced in cirrhotic patients and in neonates. Half-life is not altered significantly by renal insufficiency or hemodialysis, and dosage adjustment usually is not required. However, if the dose of chloramphenicol has been reduced because of cirrhosis, clearance by hemodialysis may be significant. This effect can be minimized by administering the drug at the end of hemodialysis. Significant variability in the metabolism and pharmacokinetics of chloramphenicol in neonates, infants, and children necessitates monitoring of drug concentrations in plasma.

Therapeutic Uses and Dosage. Therapy with chloramphenicol must be limited to infections for which the benefits of the drug outweigh the risks of the potential toxicities. When other antimicrobial drugs that are equally effective and potentially less toxic are available, they should be used instead of chloramphenicol (Wareham and Wilson, 2002).

Typhoid Fever. Third-generation cephalosporins and quinolones are drugs of choice for the treatment of typhoid f[illegible]y are

less toxic and because strains of *Salmonella typhi* often are resistant to chloramphenicol (Parry, 2003).

The adult dose of chloramphenicol for typhoid fever is 1 g every 6 hours for 4 weeks. Although intravenous and oral routes have been used, the response is more rapid with oral administration. Provided that the primary isolate is sensitive, relapses respond satisfactorily to retreatment.

Bacterial Meningitis. Third-generation cephalosporins have replaced chloramphenicol in the therapy of bacterial meningitis (Quagliarello and Scheld, 1997). Chloramphenicol remains an alternative drug for the treatment of meningitis caused by *H. influenzae*, *N. meningitidis*, and *S. pneumoniae* in patients who have severe allergy to β-lactams and in developing countries (Fuller et al., 2003). The total daily dose for children should be 50 mg/kg of body weight, divided into four equal doses given intravenously every 6 hours. Results with chloramphenicol used for pneumococcal meningitis may be unsatisfactory because some strains are inhibited but not killed. Moreover, penicillin-resistant strains frequently also are resistant to chloramphenicol (Hoban et al., 2001). In the rare situation in which chloramphenicol must be used to treat pneumococcal meningitis, lumbar puncture should be repeated 2-3 days after treatment is initiated to ensure that an adequate response has occurred.

Rickettsial Diseases. The tetracyclines usually are the preferred agents for the treatment of rickettsial diseases. However, in patients allergic to these drugs, in those with reduced renal function, in pregnant women, and in children <8 years of age who require prolonged or repeated courses of therapy, chloramphenicol may be the drug of choice. Rocky Mountain spotted fever, epidemic, murine, scrub, and recrudescent typhus, and Q fever respond well to chloramphenicol. For adults and children with these diseases, a dosage of 50 mg/kg/day divided into 6-hour intervals is recommended. For severe or resistant infections, doses up to 100 mg/kg/day may be used for short intervals, but the dose be reduced to 50 mg/kg/day as soon as possible. Therapy should be continued until the general condition has improved and the patient is afebrile for 24-48 hours.

Untoward Effects. Chloramphenicol inhibits the synthesis of proteins of the inner mitochondrial membrane, probably by inhibiting the ribosomal peptidyltransferase. These include subunits of cytochrome *c* oxidase, ubiquinone-cytochrome *c* reductase, and the proton-translocating ATPase critical for aerobic metabolism. Much of the toxicity observed with this drug can be attributed to these effects.

Hypersensitivity Reactions. Although relatively uncommon, macular or vesicular skin rashes result from hypersensitivity to chloramphenicol. Fever may appear simultaneously or be the sole manifestation. Angioedema is a rare complication. Jarisch-Herxheimer reactions may occur after institution of chloramphenicol therapy for syphilis, brucellosis, and typhoid fever.

Hematological Toxicity. The most important adverse effect of chloramphenicol is on the bone marrow. Chloramphenicol affects the hematopoietic system in two ways: a dose-related toxicity that presents as anemia, leukopenia, or thrombocytopenia, and an idiosyncratic response manifested by aplastic anemia, leading in many cases to fatal pancytopenia. Pancytopenia seems to occur more commonly in individuals who undergo prolonged therapy and especially in those who are exposed to the drug on more than one occasion. A genetic predisposition is suggested by the occurrence of pancytopenia in identical twins. Although the incidence of the reaction is low, ~1 in ≥30,000 courses of therapy, the fatality rate is high when bone marrow aplasia is complete, and there is an increased incidence of acute leukemia in those who recover. Aplastic anemia accounts for ~70% of cases of blood dyscrasias due to chloramphenicol; hypoplastic anemia, agranulocytosis, and thrombocytopenia make up the remainder. The exact biochemical mechanism has not yet been elucidated but is hypothesized to involve conversion of the nitro group to a toxic intermediate by intestinal bacteria.

The risk of aplastic anemia does not contraindicate the use of chloramphenicol in situations in which it may be lifesaving. The drug should never be used, however, in undefined situations or in diseases readily, safely, and effectively treatable with other antimicrobial agents.

Dose-related, reversible erythroid suppression probably reflects an inhibitory action of chloramphenicol on mitochondrial protein synthesis in erythroid precursors, which in turn impairs iron incorporation into heme. Leukopenia and thrombocytopenia also may occur. Bone marrow suppression occurs regularly when plasma concentrations are ≥25 μg/mL and is observed with the use of large doses of chloramphenicol, prolonged treatment, or both. Dose-related suppression of the bone marrow may progress to fatal aplasia if treatment is continued, but most cases of bone marrow aplasia develop suddenly, without prior dose-related marrow suppression. Some patients who developed chronic bone marrow hypoplasia after chloramphenicol treatment subsequently developed acute myeloblastic leukemia. The administration of chloramphenicol in the presence of hepatic disease frequently depresses erythropoiesis. About one-third of patients with severe renal insufficiency exhibit the same reaction.

Other Toxic and Irritative Effects. Nausea and vomiting, unpleasant taste, diarrhea, and perineal irritation may follow the oral administration of chloramphenicol. Blurring of vision and digital paresthesias may rarely occur. Tissues that have a high rate of oxygen consumption may be particularly susceptible to chloramphenicol effects on mitochondrial enzyme systems; encephalopathy and cardiomyopathy have been reported.

Neonates, especially if premature, may develop a serious illness termed *gray baby syndrome* if exposed to excessive doses of chloramphenicol. This syndrome usually begins 2-9 days (average of 4 days) after treatment is started. Within the first 24 hours, vomiting, refusal to suck, irregular and rapid respiration, abdominal distention, periods of cyanosis, and passage of loose green stools occur. The children all are severely ill by the end of the first day, and in the next 24 hours turn an ashen-gray color and become flaccid and hypothermic. A similar "gray syndrome" has been reported in adults who were accidentally overdosed with the drug. Death occurs in ~40% of patients within 2 days of initial symptoms. Those who recover usually exhibit no sequelae.

Two mechanisms apparently are responsible for chloramphenicol toxicity in neonates: (1) a developmental deficiency of glucuronyl transferase, the hepatic enzyme that metabolizes chloramphenicol, in the first 3-4 weeks of life; and (2) inadequate renal excretion of unconjugated drug. At the onset of the clinical syndrome, chloramphenicol concentrations in plasma usually exceed 100 μg/mL, although they may be as low as 75 μg/mL. Children ≤2 weeks of age should receive chloramphenicol in a daily dose no larger than 25 mg/kg of body weight; after this age, full-term infants may be given daily quantities up to 50 mg/kg. Toxic effects have not been ob[illegible] newborns when as much as 1 g of the antibiotic has b[illegible]ours to the mothers during labor.

Drug Interactions. Chloramphenicol inhibits hepatic CYPs and thereby prolongs the half-lives of drugs that are metabolized by this system, including warfarin, dicumarol, phenytoin, chlorpropamide, antiretroviral protease inhibitors, rifabutin, and tolbutamide. Severe toxicity and death have occurred because of failure to recognize such effects. Conversely, other drugs may alter the elimination of chloramphenicol. Concurrent administration of phenobarbital or rifampin, which potently induce CYPs, shortens the $t_{1/2}$ of the antibiotic and may result in subtherapeutic drug concentrations.

MACROLIDES AND KETOLIDES

Erythromycin was discovered in 1952 by McGuire and coworkers in the metabolic products of a strain of *Streptomyces erythreus*. Clarithromycin (BIAXIN, others) and azithromycin (ZITHROMAX, others) are semisynthetic derivatives of erythromycin. Ketolides are semisynthetic derivatives of erythromycin with activity against some macrolide-resistant strains. Telithromycin (KETEK) is the only ketolide currently approved in the U.S. Although the ketolides are promising agents against drug-resistant organisms, substantial hepatotoxicity seen with telithromycin has limited their use.

Macrolide antibiotics contain a many-membered ng (14-membered rings for erythromycin and clarithrom nd a 15-membered ring for azithromycin) to which are attached one or