

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

VOLUME 33, NUMBER 12

DECEMBER 2012

ORIGINAL ARTICLES

- 1185 Effective Antimicrobial Stewardship in a Long-Term Care Facility through an Infectious Disease Consultation Service: Keeping a LID on Antibiotic Use** • Robin L. P. Jump, MD, PhD; Danielle M. Olds, RN, PhD; Nasim Seifi, MS; Georgios Kypriotakis, MS; Lucy A. Jury, RN, CNP; Emily P. Peron, PharmD; Amy A. Hirsch, PharmD; Paul E. Drawz, MD; Brook Watts, MD; Robert A. Bonomo, MD; Curtis J. Donskey, MD
- 1193 Transfer from High-Acuity Long-Term Care Facilities Is Associated with Carriage of *Klebsiella pneumoniae* Carbapenemase-Producing *Enterobacteriaceae*: A Multihospital Study** • Kavitha Prabaker, MD; Michael Y. Lin, MD, MPH; Margaret McNally, RN, BSN, PCCN; Kartikeya Cherabuddi, MD; Sana Ahmed, MD; Andrea Norris, DO; Karen Lolans, BS; Ruba Odeh, DO; Vishnu Chundi, MD; Robert A. Weinstein, MD; Mary K. Hayden, MD; for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program
- 1200 Device-Associated Infections among Neonatal Intensive Care Unit Patients: Incidence and Associated Pathogens Reported to the National Healthcare Safety Network, 2006–2008** • Susan N. Hogevar, MD; Jonathan R. Edwards, MStat; Teresa C. Horan, MPH; Gloria C. Morrell, RN; Martha Iwamoto, MD; Fernanda C. Lessa, MD, MPH
- 1207 Incidence, Secular Trends, and Outcomes of Prosthetic Joint Infection: A Population-Based Study, Olmsted County, Minnesota, 1969–2007** • Geoffrey Tsaras, MD, MPH; Douglas R. Osmon, MD, MPH; Tad Mabry, MD; Brian Lahr, MS; Jennifer St. Sauveur, PhD; Barbara Yawn, MD; Robert Kurland, MD; Elie F. Berbari, MD
- 1213 On the Role of Length of Stay in Healthcare-Associated Bloodstream Infection** • Christie Y. Jeon, ScD; Matthew Neidell, PhD; Haomiao Jia, PhD; Matt Sinisi, MA; Elaine Larson, PhD, RN
- 1219 Identifying the Risk Factors for Hospital-Acquired Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infection among Patients Colonized with MRSA on Admission** • Yuriko Fukuta, MD; Candace A. Cunningham, RN; Patricia L. Harris, RN, MSN; Marilyn M. Wagener, MPH; Robert R. Muder, MD
- 1226 Cost-Effectiveness of Different Screening Strategies (Single or Dual) for the Diagnosis of Tuberculosis Infection in Healthcare Workers** • M. Teresa del Campo, MD, PhD; Hadia Fouad, MD; M. Marcela Solís-Bravo, MD; M. Angeles Sánchez-Uriz, MD; Ignacio Mahillo-Fernández, PhD, MSc; Jaime Esteban, MD, PhD

COMMENTARY

- 1235 Infections Associated with Use of Ultrasound Transmission Gel: Proposed Guidelines to Minimize Risk** • Susan C. Oleszkowicz, MPH; Paul Chittick, MD; Victoria Russo, MPH; Paula Keller, MS; Matthew Sims, MD, PhD; Jeffrey Band, MD



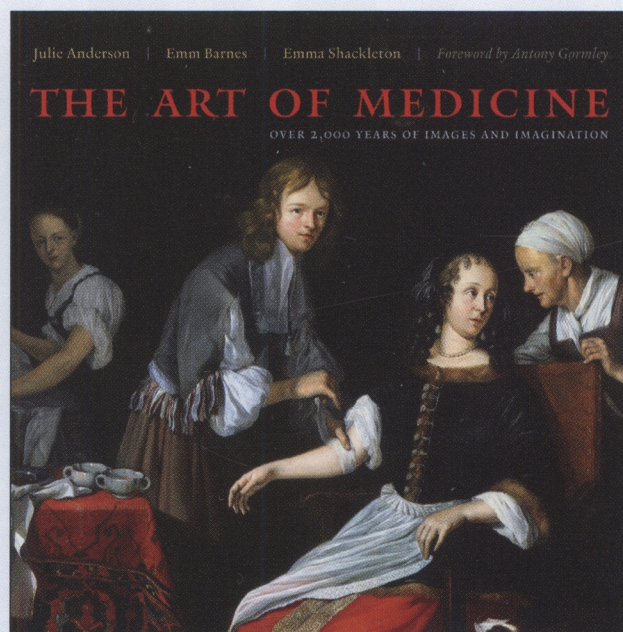
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CONTENTS CONTINUED INSIDE

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INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

VOLUME 33, NUMBER 12

DECEMBER 2012

CONTENTS CONTINUED FROM COVER

CONCISE COMMUNICATIONS

- 1238 ***Gordonia bronchialis* Sternal Wound Infection in 3 Patients following Open Heart Surgery: Intraoperative Transmission from a Healthcare Worker** • Shaneka N. Wright, RN, BSN, MHSc, CIC; Joanna S. Gerry, DNP, ARNP; Mary T. Busowski, MD; Alena Y. Klochko, MD; Steven G. McNulty, BS; Scott A. Brown, RN, MBA, CIC; Barry E. Sieger, MD; P. Ken Michaels, DO; Mark R. Wallace, MD
- 1242 **Risk Factors for Gastrointestinal Tract Colonization with Extended-Spectrum β -Lactamase (ESBL)-Producing *Escherichia coli* and *Klebsiella* Species in Hospitalized Patients** • Jennifer H. Han, MD, MSCE; Irving Nachamkin, DrPH, MPH; Theoklis E. Zaoutis, MD, MSCE; Susan E. Coffin, MD, MPH; Darren R. Linkin, MD, MSCE; Neil O. Fishman, MD; Mark G. Weiner, MD; Baofeng Hu, MD; Pam Tolomeo, MPH; Ebbing Lautenbach, MD, MPH, MSCE
- 1246 **Impact of Vancomycin Minimum Inhibitory Concentration on Mortality among Critically Ill Patients with Methicillin-Resistant *Staphylococcus aureus* Bacteremia** • Christian J. Woods, MD; Anindita Chowdhury, MD; Vinay M. Patel, MD; Andrew F. Shorr, MD, MPH
- 1250 **Epidemiology of Vancomycin-Resistant Enterococci with Reduced Susceptibility to Daptomycin** • Theresa Judge, PharmD; Jason M. Pogue, PharmD; Dror Marchaim, MD; Kevin Ho, BA; Srinivasa Kamatam, MBBS; Shakila Parveen, MBBS; Namita Tiwari, MBBS; Priyanka Nanjireddy, MBBS; Suchitha Bheemreddy, MBBS; Caitlin Biedron, MS; Sagar Mallikethi Lepakshi Reddy, MBBS; Vijaykumar Khammam; Indu K. Chalana, MBBS; Rajachendra Shekher Tumma, MBBS; Vicki Collins, MD, MPH; Adnan Yousuf, MD; Paul R. Lephart, PhD; Emily T. Martin, PhD; Michael J. Rybak, PharmD, MPH; Keith S. Kaye, MD, MPH; Kayoko Hayakawa, MD, PhD
- 1255 **Efficacy of Different Cleaning and Disinfection Methods against *Clostridium difficile* Spores: Importance of Physical Removal versus Sporicidal Inactivation** • William A. Rutala, PhD, MPH; Maria F. Gergen, MT (ASCP); David J. Weber, MD, MPH
- 1259 **The Precision of Human-Generated Hand-Hygiene Observations: A Comparison of Human Observation with an Automated Monitoring System** • Deepti Sharma, BS; Geb W. Thomas, PhD; Eric D. Foster, PhD; Jaclyn Iacovelli, MS; Krista M. Lea; Judy A. Streit, MD; Philip M. Polgreen, MD, MPH
- 1262 **Current Approach to Latent Tuberculosis Diagnosis and Treatment among Medical Center Occupational Health Physicians** • Christopher Vinnard, MD, MPH, MSCE; Darren Linkin, MD, MSCE; Amy Behrman, MD

RESEARCH BRIEFS

- 1266 **Black-Water Floods and Hospital-Based Postflood Mold Investigations** • Anucha Apisarnthanarak, MD; Thana Khawcharoenporn, MD, MSc; Linda M. Mundy, MD, PhD
- 1268 **Intensity of Vascular Catheter Use in Critical Care: Impact on Catheter-Associated Bloodstream Infection Rates and Association with Severity of Illness** • Kimberlee S. Fong, MD; Mary Banks, BS; Rebekah Benish, BA; Cynthia Fatica, RN, BSN, CIC; Melissa Triche, BA; Nehemiah Smith, MHSA; Robert Butler, MS; Steven M. Gordon, MD; Thomas G. Fraser, MD
- 1270 **Natural Language Processing to Identify Foley Catheter-Days** • Valmeek Kudesia, MD; Judith Strymish, MD; Leonard D'Avolio, PhD; Kalpana Gupta, MD, MPH

CONTENTS CONTINUED ON NEXT PAGE

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

VOLUME 33, NUMBER 12

DECEMBER 2012

CONTENTS CONTINUED FROM PREVIOUS PAGE

- 1272 National Survey of Infection Preventionists: Policies for Discontinuation of Contact Precautions for Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant Enterococcus** • Erica S. Shenoy, MD, PhD; Heather Hsu, MPH; Farzad Noubary, PhD; David C. Hooper, MD; Rochelle P. Walensky, MD, MPH
- 1276 Descriptive Analysis of Healthcare-Associated Infections Other than Bloodstream, Respiratory, Urinary Tract, or Surgical Site Infections, 2001–2011** • Hajime Kanamori, MD, PhD; David J. Weber, MD, MPH; Emily E. Sickbert-Bennett, PhD; Vickie Brown, RN, MPH; Mitsuo Kaku, MD, PhD; William A. Rutala, PhD, MPH
- 1277 The Influence of Environmental Temperature and Air Humidity on the Maintenance of Sterility of Surgical Instruments Sterilized in Different Wraps** • Camila Quartim de Moraes Bruna, MS; Flávia Morais Gomes Pinto, MS; Kazuko Uchikawa Graziano, PhD
- 1280 Safety Culture and Hand Hygiene: Linking Attitudes to Behavior** • Elizabeth Lee Daugherty, MD, MPH; Lori A. Paine, RN, MS; Lisa L. Maragakis, MD, MPH; J. Bryan Sexton, PhD; Cynthia S. Rand, PhD
- 1282 Do Patients Feel Comfortable Asking Healthcare Workers to Wash Their Hands?** • Andrew Ottum, MPH; Ajay K. Sethi, PhD, MHS; Elizabeth A. Jacobs, MD, MPP; Sara Zerbel, MS; Martha E. Gaines, JD, LLM; Nasia Safdar, MD, PhD

LETTERS TO THE EDITOR

- 1285 Air Quality of a Hospital after Closure for Black-Water Flood: An Occupational-Health Concern?** • Anucha Apisarnthanarak, MD; Thana Khawcharoenporn, MD, MSc; Linda M. Mundy, MD, PhD
- 1286 Variability of Adenosine Triphosphate–Based Bioluminescence Assay Readings among Drug-Resistant Pathogens** • Michaela Heller, BS; Paul A. Thompson, PhD; Mark H. Looock, BS; Ander Sawchuk; Dubert M. Guerrero, MD
- 1288 Increasing Influenza Vaccination Rates among Hospital Employees without a Mandatory Policy** • Rohit M. Modak, MD, MBA; Sarah M. Parris, RN, MSN, COHN; Jeffrey P. Dilisi, MD, MBA; Ajay Premkumar, BS
- 1290 Reviewers for Volume 33**
- 1292 Author Index**

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3rd edition

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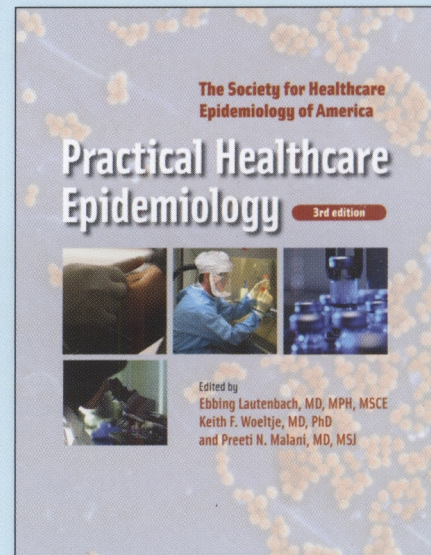
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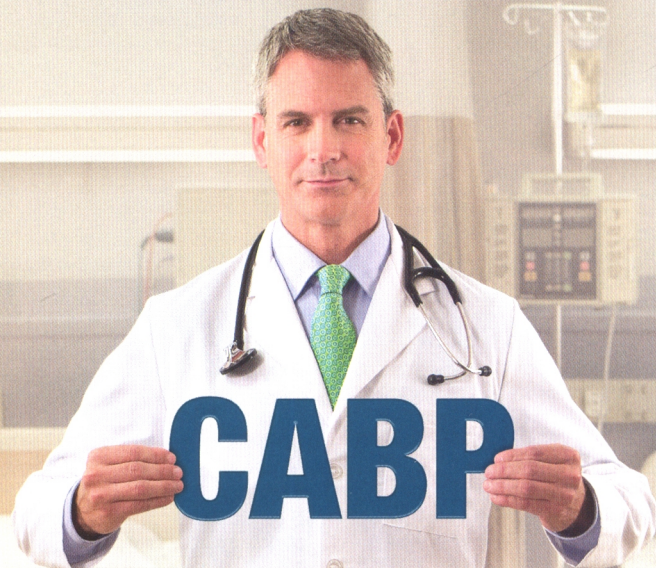
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- When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

INDICATION

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IMPORTANT SAFETY INFORMATION

Contraindications

- TEFLARO is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

Warnings and Precautions

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- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported with beta-lactam antibacterials. Before therapy with TEFLARO is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.
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- To reduce the development of drug-resistant bacteria and maintain the effectiveness of TEFLARO and other antibacterial drugs, TEFLARO should be used to treat only CABP that is proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

IMPORTANT SAFETY INFORMATION (continued)

***Clostridium difficile*-associated Diarrhea**

- Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including TEFLARO, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible.

Direct Coombs' Test Seroconversion

- Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving TEFLARO and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with TEFLARO, drug-induced hemolytic anemia should be considered. If drug-induced hemolytic anemia is suspected, discontinuation of TEFLARO should be considered and supportive care should be administered to the patient if clinically indicated.

Development of Drug-Resistant Bacteria

- Prescribing TEFLARO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adverse Reactions

- In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving TEFLARO and 100/1297 (7.7%) of patients receiving comparator drugs. Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving TEFLARO and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the TEFLARO group and 0.5% in the comparator group.
- No adverse reactions occurred in greater than 5% of patients receiving TEFLARO. The most common adverse reactions occurring in >2% of patients receiving TEFLARO in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash.

Drug Interactions

- No clinical drug-drug interaction studies have been conducted with TEFLARO. There is minimal potential for drug-drug interactions between TEFLARO and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow.

Use in Specific Populations

- TEFLARO has not been studied in pregnant women. Therefore, TEFLARO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
- It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEFLARO is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Because elderly patients, those ≥ 65 years of age, are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Dosage adjustment for elderly patients should therefore be based on renal function.
- Dosage adjustment is required in patients with moderate (CrCl >30 to ≤ 50 mL/min) or severe (CrCl ≥ 15 to ≤ 30 mL/min) renal impairment and in patients with end-stage renal disease (CrCl ≤ 15 mL/min).
- The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.

Please see brief summary of Prescribing Information on following page.
Please also see full Prescribing Information at www.TEFLARO.com.



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INDICATIONS AND USAGE: Teflaro® (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms. **Acute Bacterial Skin and Skin Structure Infections** - Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. **Community-Acquired Bacterial Pneumonia** - Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*. **Usage** - To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used to treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS: Teflaro is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions - Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterials. Before therapy with Teflaro is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established. If an allergic reaction to Teflaro occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated. **Clostridium difficile-associated Diarrhea** - *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Teflaro, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated [see *Adverse Reactions*]. **Direct Coombs' Test Seroconversion** - Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving Teflaro and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. In the pooled Phase 3 CABP trials, 51/520 (9.8%) of Teflaro-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with Teflaro, drug-induced hemolytic anemia should be considered. Diagnostic studies including a direct Coombs' test, should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of Teflaro should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated. **Development of Drug-Resistant Bacteria** - Prescribing Teflaro in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS: The following serious events are described in greater detail in the Warnings and Precautions section: Hypersensitivity reactions; *Clostridium difficile*-associated diarrhea; Direct Coombs' test seroconversion. **Adverse Reactions from Clinical Trials** - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice. Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CABP) which included 1300 adult patients treated with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone) for a treatment period up to 21 days. The median age of patients treated with Teflaro was 54 years, ranging between 18 and 99 years old. Patients treated with Teflaro were predominantly male (63%) and Caucasian (82%). **Serious Adverse Events and Adverse Events Leading to Discontinuation** - In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving Teflaro and 100/1297 (7.7%) of patients receiving comparator drugs. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system organ classes (SOC). Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving Teflaro and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the Teflaro group and 0.5% in comparator group. **Most Common Adverse Reactions** - No adverse reactions occurred in greater than 5% of patients receiving Teflaro. The most common adverse

reactions occurring in > 2% of patients receiving Teflaro in the pooled phase 3 clinical trials were diarrhea, nausea, and rash. Table 4 in the full prescribing information lists adverse reactions occurring in ≥ 2% of patients receiving Teflaro in the pooled Phase 3 clinical trials (two in ABSSSI and two in CABP). The first value displays the percentage of patients in the pooled Teflaro trials (N=1300) and the second shows the percentage in the Pooled Comparators[†] trials (N=1297). **Gastrointestinal disorders:** Diarrhea (5%, 3%), Nausea (4%, 4%), Constipation (2%, 2%), Vomiting (2%, 2%); **Investigations:** Increased transaminases (2%, 3%); **Metabolism and nutrition disorders:** Hypokalemia (2%, 3%); **Skin and subcutaneous tissue disorders:** Rash (3%, 2%); **Vascular disorders:** Phlebitis (2%, 1%) * Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials. **Other Adverse Reactions Observed During Clinical Trials of Teflaro** - Following is a list of additional adverse reactions reported by the 1740 patients who received Teflaro in any clinical trial with incidences less than 2%. Events are categorized by System Organ Class. **Blood and lymphatic system disorders** - Anemia, Eosinophilia, Neutropenia, Thrombocytopenia; **Cardiac disorders** - Bradycardia, Palpitations; **Gastrointestinal disorders** - Abdominal pain; **General disorders and administration site conditions** - Pyrexia; **Hepatobiliary disorders** - Hepatitis; **Immune system disorders** - Hypersensitivity, Anaphylaxis; **Infections and infestations** - *Clostridium difficile* colitis; **Metabolism and nutrition disorders** - Hyperglycemia, Hyperkalemia; **Nervous system disorders** - Dizziness, Convulsion; **Renal and urinary disorders** - Renal failure; **Skin and subcutaneous tissue disorders** - Urticaria.

DRUG INTERACTIONS: No clinical drug-drug interaction studies have been conducted with Teflaro. There is minimal potential for drug-drug interactions between Teflaro and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow [see *Clinical Pharmacology*].

USE IN SPECIFIC POPULATIONS: Pregnancy Category B. - Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats (based on AUC) at this dose level was approximately 8 times the exposure in humans given 600 mg every 12 hours. There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at ≥ 50 mg/kg; these were associated with an increase in spontaneous abortion at 50 and 100 mg/kg. The highest dose was also associated with maternal morbidity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic doses of 50 and 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was approximately 0.8 times the exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg. Ceftaroline fosamil did not affect the postnatal development or reproductive performance of the offspring of rats given IV doses up to 450 mg/kg/day. Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was ≥ 8 times the exposure in humans given 600 mg every 12 hours. There are no adequate and well-controlled trials in pregnant women. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** - It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Teflaro is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** - Of the 1300 patients treated with Teflaro in the Phase 3 ABSSSI and CABP trials, 397 (30.5%) were ≥ 65 years of age. The clinical cure rates in the Teflaro group (Clinically Evaluable [CE] Population) were similar in patients ≥ 65 years of age compared with patients < 65 years of age in both the ABSSSI and CABP trials. The adverse event profiles in patients ≥ 65 years of age and in patients < 65 years of age were similar. The percentage of patients in the Teflaro group who had at least one adverse event was 52.4% in patients ≥ 65 years of age and 42.8% in patients < 65 years of age for the two indications combined. Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Elderly subjects had greater ceftaroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However, higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based on renal function [see *Dosage and Administration and Clinical Pharmacology*]. **Patients with Renal Impairment** - Dosage adjustment is required in patients with moderate (CrCl ≥ 30 to < 50 mL/min) or severe (CrCl ≥ 15 to < 30 mL/min) renal impairment and in patients with end-stage renal disease (ESRD - defined as CrCl < 15 mL/min), including patients on hemodialysis (HD) [see *Dosage and Administration and Clinical Pharmacology*].

OVERDOSAGE: In the event of overdose, Teflaro should be discontinued and general supportive treatment given. Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use of hemodialysis to treat overdose [see *Clinical Pharmacology*].

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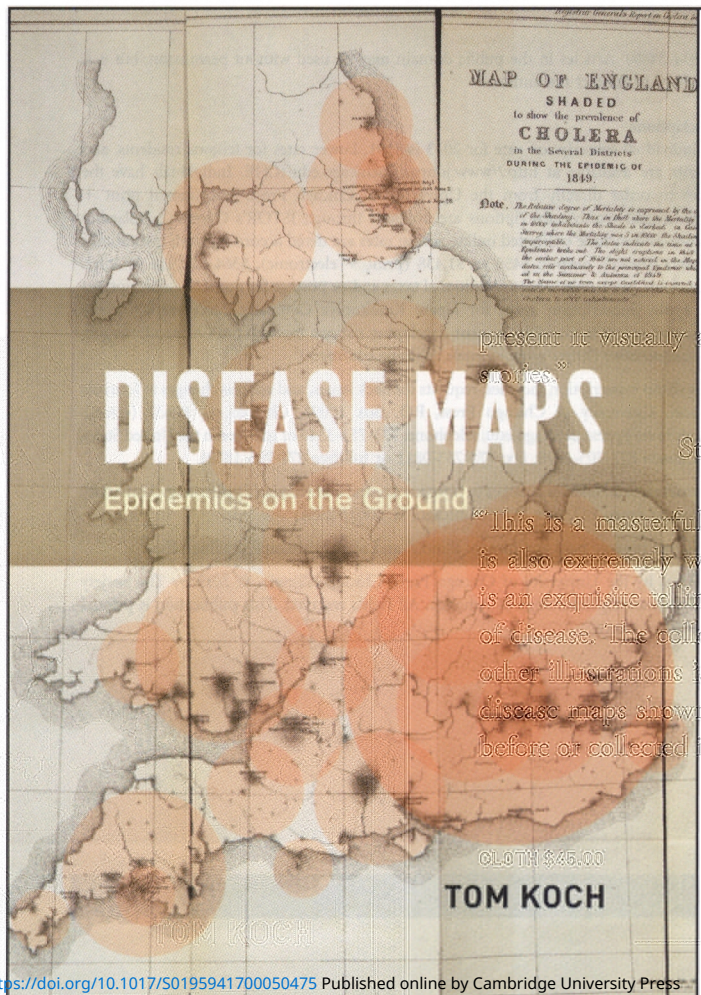
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